THE MEDICAL JOURNAL OF AUSTRALIA

VOL. II.—17TH YEAR. SYDNEY, SATURDAY, NOVEMBER 8, 1930. No. 19.

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BLOOD CELLS: RECENT ADVANCES IN EXAMINATION AND INTERPRETATION.[1]

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THE blood as a tissue was the subject of the presidential address to the Pathological Section of the Royal Society of Medicine last year. One usually regards the blood as conveying oxygen and food substances to the tissues and carrying away various waste products of cell metabolism and also having a very important function in any defensive reaction of the body. Professor Boycott[1] stressed the conception of blood as a tissue complete in itself with its own individuality. It differs from other tissues in that its constituent cells are free and in a constant state of motion; it is a labile tissue without rigidity of structure and yet has a definite conformation as determined by the walls of the blood vessels.

This individuality of the blood, manifest by a constant composition, enables us to have certain standards, departure from which is indicative of abnormality not only of the blood itself, but also of other tissues and organs. Morphologically we have standard cell counts and hæmoglobin value and the object of a routine blood examination is to determine if any deviations from the normal are present and, if so, to interpret them.

Red Blood Cell Count.

Cell counts indicate the concentration of the blood cells and in estimating the significance of an abnormal red cell count there are two important factors to be considered, namely, plasma volume and corpuscular volume. The general conception that the extent of an anæmia is represented cor-

[1] Read at a meeting of the Victorian Branch of the British Medical Association on July 2, 1930.

rectly by the red cell count is erroneous unless the total blood volume remains constant. If plasma volume remains constant and there is a fall in corpuscular volume, there will be a corresponding fall in total blood volume and the red cell count will not indicate the extent of the depletion of the red cells.

In lead poisoned rabbits I found the plasma volume to remain practically constant.[2] There was a fall in corpuscular volume which averaged 43%, while the average fall in the red cell count was 29%. At first I thought the discrepancy was due to the fact that the average diameter of the cells was reduced and so a given number of cells would occupy a smaller volume. However, Dr. Penfold pointed out that the fall in total blood volume could account for the discrepancy and when the red cell count was corrected for this shrinkage in total volume, there was a difference of only 4% in the corpuscular volume fall and the red cell count fall.

Bock[3] has shown that the plasma volume remains constant in various diseases, including polycythæmia, pernicious anæmia, heart failure with œdema, nephritis with œdema, and diabetes. In their recent book, entitled "The Volume of the Blood and Plasma in Health and Disease," Rowntree and Brown[4] state: "We believe that the plasma volume constitutes one of the most striking and significant so-called constants of the body." If the plasma volume is invariable and can be calculated with reference to body weight or body surface, then from the hæmatocrit the total corpuscular volume can be calculated. Changes in the total corpuscular volume are of much greater significance than changes in the red cell count and it is possible that hæmatocrit determinations will at some future date be included in routine blood examinations.

Estimation of Hæmoglobin.

Routine blood examinations usually include an estimation of hæmoglobin and in the diagnosis of various anæmias the clinician is to a great extent dependent upon a fairly accurate determination. There are many methods for hæmoglobin estimation, but none of them is entirely satisfactory. Most are colorimetric and the standards employed are subject to variation in different instruments, while the individual experimental error is certainly to be considered.

Haldane's carbon monoxide method gives results which have been estimated to be accurate to 5% if the standards are fresh, but the method has not found general clinical use, as coal gas is not always available.

In the Sahli method the hæmoglobin is converted to brown acid hæmatin by the addition of decinormal hydrochloric acid and the colour produced is compared with a standard. One of the chief disadvantages of this method is that the colour of the standard solution fades on keeping and efforts have been made to overcome this defect by substituting coloured glass standards. In 1900 Tallquist[5] devised the simple procedure of blotting up a drop of blood on a filter paper and comparing the colour with a series of standard shades.

Table I shows hæmoglobin estimations by these three methods in a small series of cases. It will be observed that there are quite marked differences and with the Tallquist method I was unable to obtain a value below 60%, although the corresponding Haldane and Sahli results were in quite a few cases below 40%. It is generally accepted that the Tallquist is a crude method, and personally I think it should be discarded.

TABLE I.

Disease.	Haldane.	Sahli.	Tallquist.
	%	%	%
Pernicious anæmia	35	32	70
Pernicious anæmia	65	62	75
Pernicious anæmia	31	30	70
Subacute combined degeneration	85	80	80
Myeloid leuchæmia	85	82	80
Myeloid leuchæmia	—	60	70
Lymphatic leuchæmia	32	28	70
Lymphatic leuchæmia	33	32	60
Lymphatic leuchæmia	36	39	70
Polycythæmia	134	118	100
Polycythæmia	111	105	100
Polycythæmia	140	109	100
Familial acholuric jaundice	37	33	65
Secondary anæmia	63	55	55
Secondary anæmia	58	50	70
Secondary anæmia	73	65	70
Normal	82	75	75
Normal	93	82	80
Normal	84	80	75
Normal	84	75	75
Normal	98	85	85
Normal	87	73	80
Normal	87	72	80
Normal	72	70	80

An accurate determination of hæmoglobin may be made by measuring the oxygen capacity of the blood, as it has been shown that one gramme of hæmoglobin combines with 1·34 cubic centimetres of oxygen. Haldane and Smith[6] were the first to apply an accurate method to the determination of the oxygen capacity of the blood. More recently Van Slyke[7] has modified the process and with his method experimental error has been reduced to 0·48%.

TABLE II.

Blood Film.	Number of Cases.	Pijper's Diffraction Micrometer.		Eve's Halometer.		
		Average Diameter of Halo in Millimetres.	Average Width of Spectrum in Millimetres.	Average Reading.	Maximum Reading.	Minimum Reading.
Normal	50	80	20	4·8°	5·0°	4·5°
Secondary anæmia	178	79	19·9	4·7°	5·6°	4·35°
Pernicious anæmia	22	66	16·5	4·1°	4·3°	3·9°

Hæmoglobin can also be estimated by determining the iron content of the blood, as it has been shown that hæmoglobin contains 0·334% of its total weight of iron. This method is subject to a 1% experimental error. Both the oxygen and iron capacity methods are too difficult and tedious for ordinary routine clinical work, but, nevertheless, find a useful purpose in standardizing the less accurate clinical instruments.

Recently, in the Physiological Laboratory of the Johns Hopkins Hospital,[8] a spectroscope method for the determination of hæmoglobin has been devised which is simple, very accurate and rapid, with an experimental error estimated at less than 0·7%. If this instrument fulfils all the claims made for it, it should become the standard instrument for hæmoglobin determination.

White Blood Cell Count.

With regard to the white blood cell count, it is important to recognize the normal physiological variation. Dr. K. D. Fairley[9] has estimated this variation to be probably between 4,500 and 15,000 leucocytes per cubic millimetre. More recently Shaw[10] has shown that a marked diurnal variation in the leucocyte count occurs in the normal individual. He has demonstrated the presence of leucocyte tides, the flood tides occurring in the early hours after midnight and in the afternoon, and these tides occur regardless of food, exercise or sleep. The significance of this phenomenon is unknown, but the important fact to be remembered is that there is a definite variation in the leucocyte count in the normal individual and the time at which a count is made is a significant factor.

The Halo Phenomenon.

More than a century ago Thomas Young made use of the phenomenon of diffraction of light to measure the size of small objects, such as vegetable spores, blood cells and fine threads of fabrics. He named his instrument the "eriometer" or wool measurer. Independently in 1918 a South African pathologist named Pijper,[11] while investigating pigmented bacterial colonies, observed a colour effect when non-pigmented colonies were looked at obliquely. This colour effect was in the nature of a halo and was produced by a diffraction phenomenon. He found that the size of the halo varied inversely with the size of the organisms in the culture and he developed a method for measuring the size of bacteria. He then applied the method to red blood cells and was able by this means to differentiate pernicious anæmia films from secondary anæmia films.[12][13] The outstanding feature of a pernicious anæmia film is the presence of megalocytes and this increased number of large red cells is manifested by a small sized halo. Figure IA represents diagrammatically the construction of Pijper's diffraction micrometer, as modified by W. Edwards.[14] The source of light, S, is at the focus of a short focal length lens, L^1. A narrow beam of parallel light emerging from a stop in front of this lens passes through a blood film, F, which acts as a diffraction grating resolving the white light into its component spectral colours. The light then passes through a long focal length lens, L^2, and a halo is represented on an opaque glass screen in the focal plane of the lens. The instrument is in reality a camera box and is partitioned off into two compartments so that the halos of two films can be shown on the screen side by side. The lower figure shows the halo of a normal film, N, and a pernicious anæmia film, P.A.

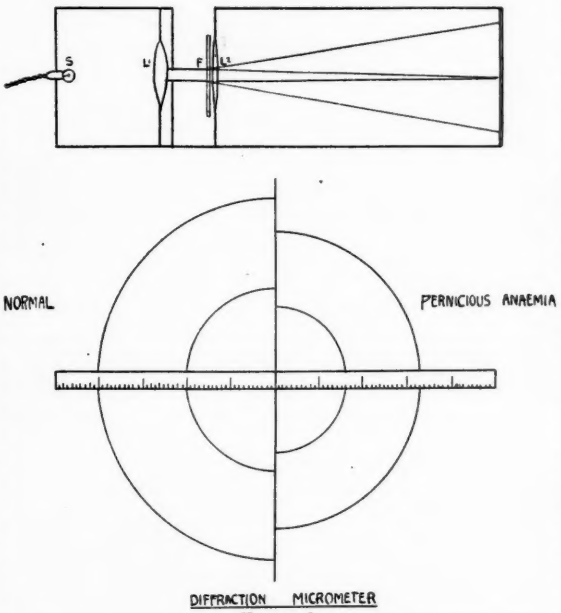


FIGURE IA.
Showing construction of Pijper's diffraction micrometer as modified by Edwards.

Eve[15] has devised a halometer in which the camera box of Pijper's diffraction micrometer is replaced by the human eye, and consequently the instrument is of very simple construction. There are two sources of light (Figure IB), S_1 and S_2, which are at a fixed distance from one another, but at a variable distance from the eye of the observer, E. The observer, looking at these two sources of light through the blood film, F, sees two halos. The distance of the sources of light from the observer is varied until the edges of the two halos are just in contact. This position is a fixed one for any particular blood film and a scale on the instrument indicates the angle subtended by the edge of the halo to the axis of the beam of light. From this reading the average diameter of the red cells in μ can be calculated by reference to a table.

The lower drawing represents halos from two films observed at the same distance from the source of light. The red edges of the halos are in contact in the normal film and this is the position at which a reading is taken. The angle subtended by the red edge of the halo to the axis of the beam of light is much smaller in the pernicious anæmia film and

the distance from the source of light would have to be increased for the red edges to be in contact.

Table II shows the average results of the examination of 245 blood films, both with Pijper's diffraction micrometer and Eve's halometer. It will be observed that all the abnormal films, whether from secondary anæmia or from pernicious anæmia, show on the average a smaller halo than normal. The secondary anæmia films show a much greater range of variation than either the normal or the pernicious anæmia films. Thus with the halometer the variation in normal films between maximum and minimum readings is 0·5°, the variation in pernicious anæmia films is 0·6°, while the variation in secondary anæmia is 1·25°. The important fact is that the halo from the pernicious anæmia film is very much smaller than the normal or secondary anæmia halo and in the twenty-two cases of pernicious anæmia the maximum reading (4·3°) is smaller than the minimum reading given by the series of 173 secondary anæmias (4·35°). The limit given by Eve for a pernicious anæmia film is 4·4° which, according to my results, is too high. With the instrument I have been using I would make the outside limit 4·3°. The results are presented in greater detail in Table III. Eve has stated that the halos given by polycythæmia and familial acholuric jaundice films are usually over 5·0°. The readings I obtained in four polycythæmic films were all below 5·0°, but the films from the cases of familial acholuric jaundice were all well above 5·0°, the minimum reading being above any maximum reading in the series.

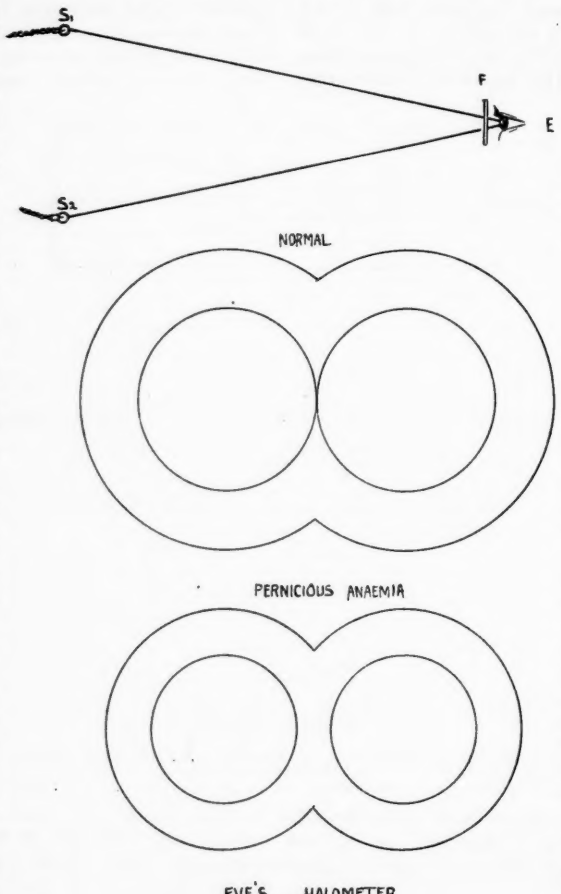


FIGURE Ib.

Showing halos as demonstrated by Pijper's diffraction micrometer and Eve's halometer.

It was interesting that of all the secondary anæmia films the lowest readings were given by conditions the diagnosis of which is apt to be confused with pernicious anæmia. Thus, proved cases of splenic anæmia, acquired acholuric jaundice, carcinoma of the stomach and anaerobe infection gave on occasion halos which were well below the normal dimensions, but, however, were definitely larger than the largest halo given by the series of pernicious anæmia films.

It would appear that Eve's halometer is a useful instrument in confirming a clinical diagnosis of pernicious anæmia and also possibly familial acholuric jaundice. In using this instrument care must be taken to prepare thin, evenly spread blood films. In several films which were unevenly spread, I found a marked difference in readings taken at different areas of the same film. Thus in three films I found differences of 0·9°, 0·5° and 0·3° respectively, the smaller readings being obtained from thick areas of the smear.

The results with Pijper's diffraction micrometer method correspond to the readings from Eve's halometer and I have not considered them in detail because of the two instruments Eve's is the more adapted to clinical use.

The Microscopy of Blood Cells.

The microscopical examination of blood covers a very wide field. I use Giemsa stain (Grübler) as a routine for blood films, both on account of its excellent qualities as a stain and because the colours do not fade. The film is fixed with pure methyl alcohol for two to five minutes, then covered with the Giemsa stain diluted one to five with neutral distilled water. After thirty minutes the stain is washed off with neutral distilled water until the film assumes a rose red colour.

Of the red blood corpuscles and their progenitors the most interesting cell is the megaloblast. This cell is found normally in fœtal blood and occasionally abnormally in post-natal life in pernicious anæmia and, according to Naegeli, is pathognomonic of this disease, but all hæmatologists do not follow Naegeli's lead in this respect. The megaloblast is found in embryonic life in the liver and, according to Piney,[16] only in the liver and never anywhere else, either in embryonic or post-natal life. Piney's hypothesis is that in pernicious anæmia there is present in the liver an embryonic remnant or entodermal *Anlage* which, given a suitable stimulus, undergoes hyperplasia and liberates megaloblasts

ILLUSTRATIONS TO THE ARTICLE BY DR. JOHN A. McLEAN.

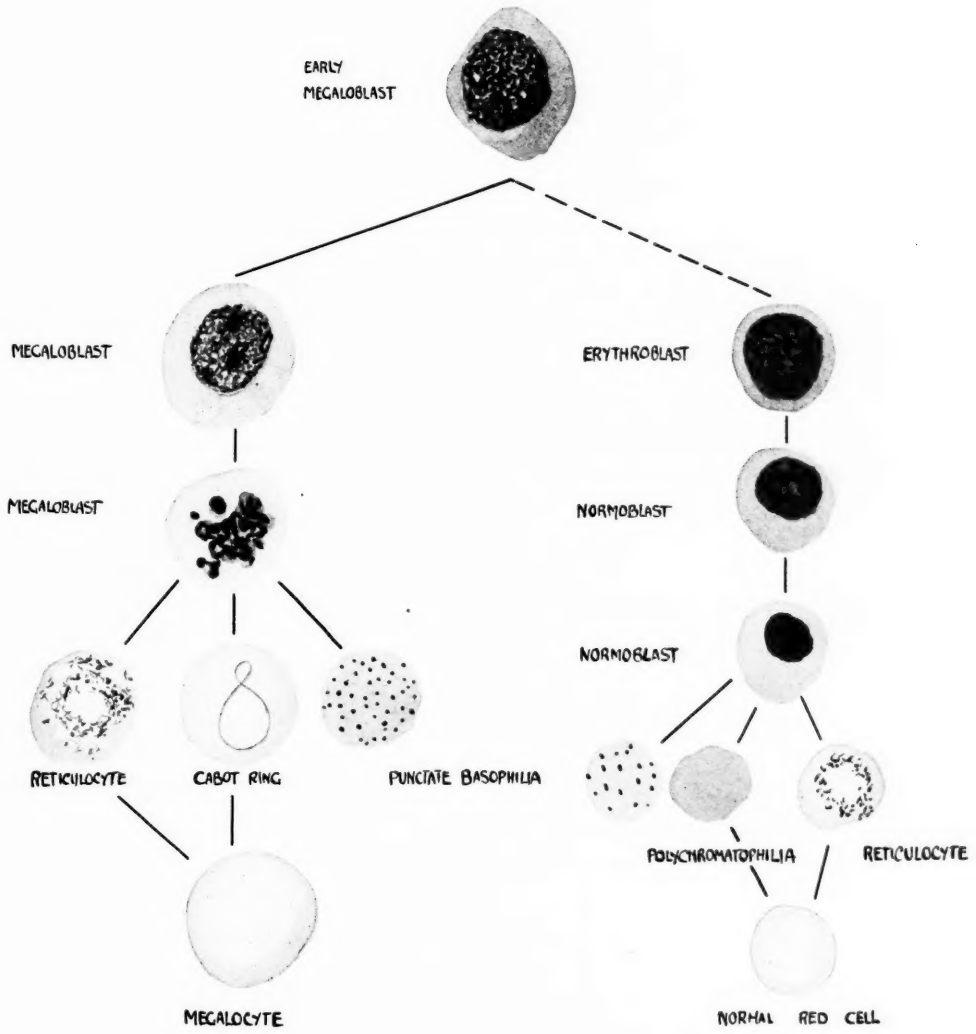


FIGURE II.
Showing development of the megalocyte from the megaloblast and the normal red cell from the erythroblast.

ILLUSTRATIONS TO THE ARTICLE BY DR. JOHN A. McLEAN.

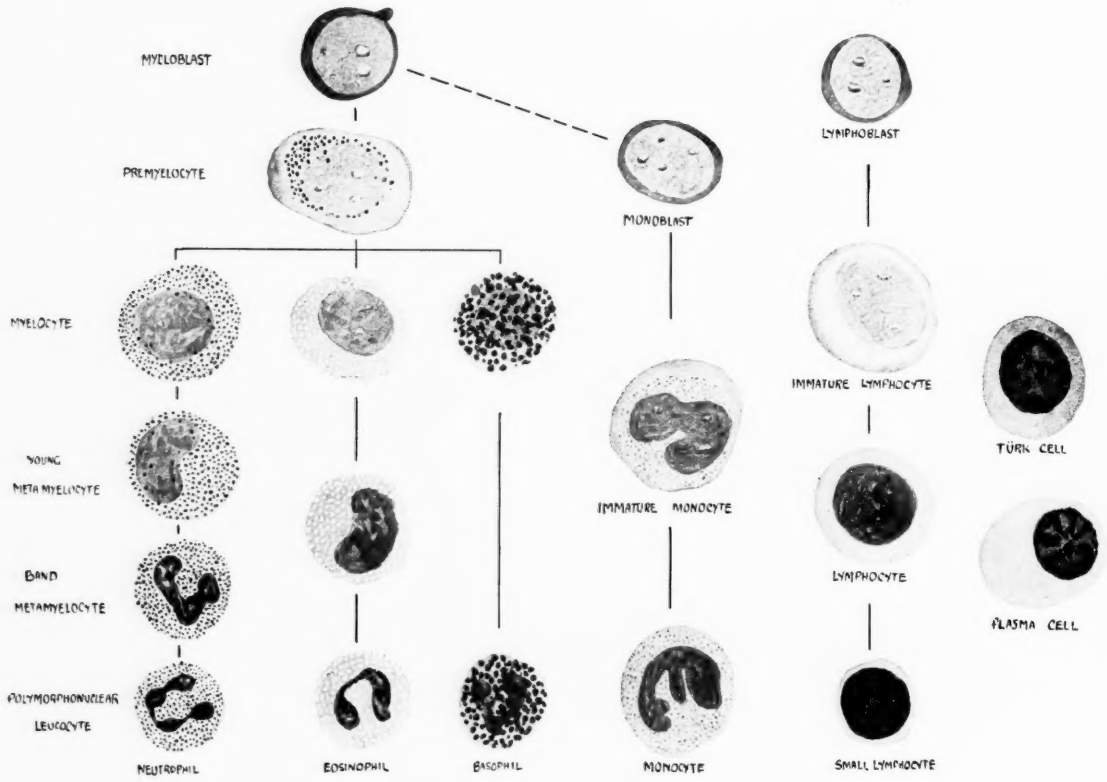


FIGURE III.
Showing white blood cells drawn from Giemsa stained blood films.

ILLUSTRATIONS TO THE ARTICLE BY DR. JOHN A. McLEAN.

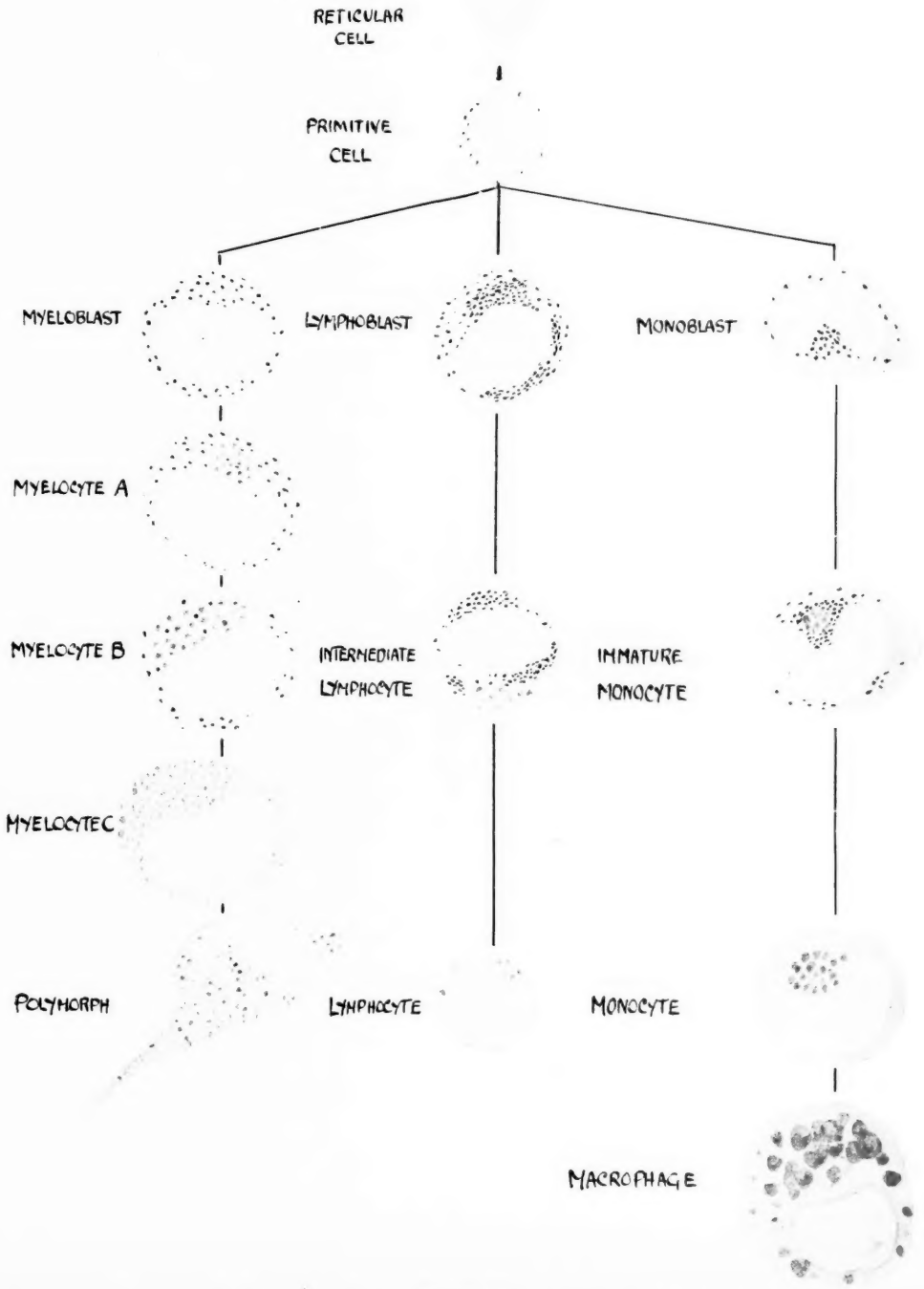


FIGURE IV.

Showing the development of white blood cells according to Cunningham, Sabin and Doan.[20] Supravital staining with neutral red and Janus green.

ILLUSTRATIONS TO THE ARTICLE BY DR. JOHN FIDDES AND DR. HENRY A. PHILLIPS.

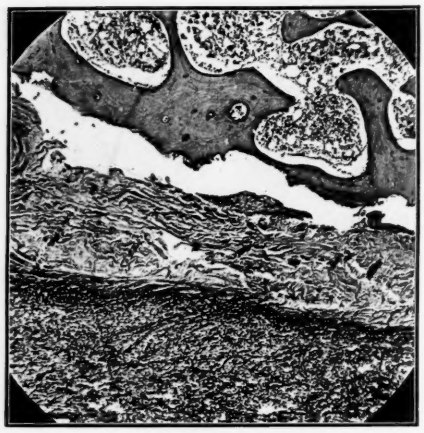
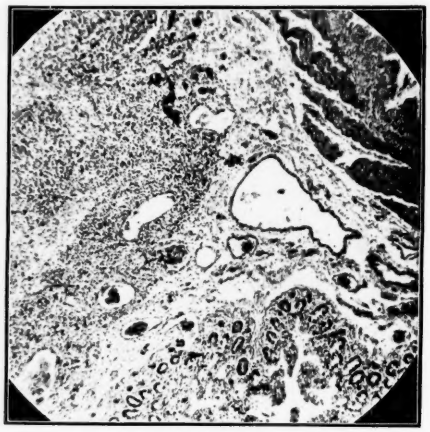


FIGURE I.



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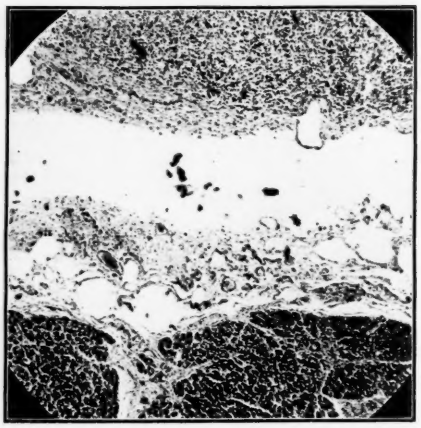

FIGURE III.

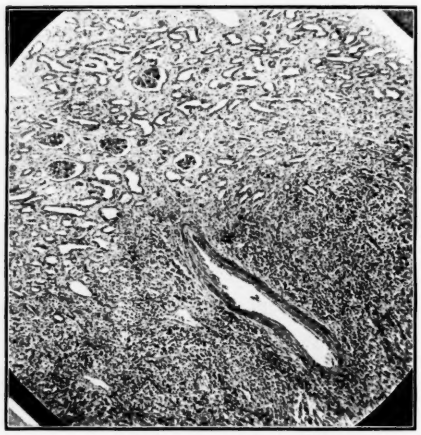

FIGURE IV.

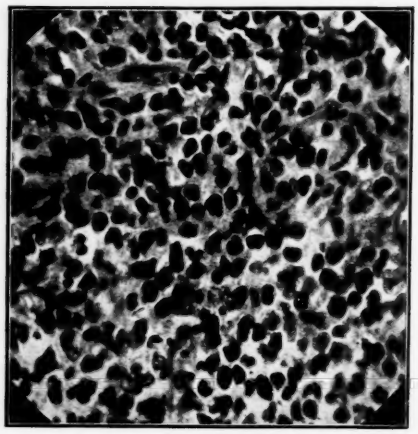

FIGURE V.

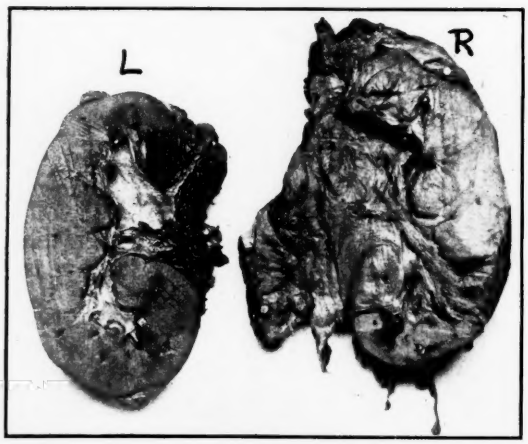

FIGURE VI.

into the peripheral circulation. However, this hypothesis is not universally accepted.

Figure II shows the development of red cells from megaloblasts and erythroblasts respectively. The term erythroblast is synonymous with the term early normoblast. The red cell derived from the megaloblast is a giant in the morphological sense and is usually termed a megalocyte. In the more immature cells the nucleus has a well defined fine chromatin structure with nucleoli and the cytoplasm takes the basic stain with only a slight slate-grey tinge from the presence of hæmoglobin. As the cell matures, the hæmoglobin increases in the cytoplasm and the nuclear chromatin becomes dense. The nucleus probably breaks up and the nuclear fragments are extruded. The erythroblast is a smaller cell than the megaloblast and the chromatin network is coarse and often has a radiating appearance, hence the term "cart wheel nucleus." The normoblast nucleus, as it becomes pyknotic and dead, is, according to the observations of Valentine,[17] probably extruded intact or rarely in two or more rounded portions.

Having lost its nucleus, but still immature in that it contains a basic staining substance in its cytoplasm, the immature red cell may be demonstrated in fixed films as a polychromatophilic cell or in vitally stained preparations as a reticulocyte. A reticulocyte is an immature red cell in which the basophilic substance has been precipitated in the living cell by a dye such as brilliant cresyl blue. Under certain circumstances the basophilic substance appears in fixed stained films as discrete granules. This phenomenon, termed punctate basophilia, has been shown to be largely determined by the manner of fixation of the blood film. Thus, in a case of lead poisoning I found in Leishman stained films 0·8% stippled cells, in Giemsa films there was 0·1% of these cells, and when the film was fixed immediately in 100% alcohol or by a temperature of 60° no stippled cells at all could be found in the film. It would appear that punctate basophilia is an artifact produced in fixation, but there is probably another factor involved which has altered the basophilic substance in some way to render it easily precipitated.

An increased number of reticulocytes in the peripheral circulation indicates active regeneration of red cells in the bone marrow. In familial acholuric jaundice the most obvious defect is an undue fragility of the mature red cells and to compensate for the curtailed existence of these cells in the peripheral circulation the bone marrow undergoes hyperplasia, as is evidenced by a very high reticulocyte count. This disease is in contrast to pernicious anæmia in which there is defective formation of red cells in the bone marrow and in the peripheral circulation a very low reticulocyte count. Chart I shows the typical reticulocyte response to liver treatment in pernicious anæmia.

This patient, a man, aged sixty-six, was extremely anæmic on admission and his was a classical case. He was given "Heparidine" liver extract which is manufactured locally, and his condition has improved remarkably.

Two cases have come under my notice in which the response to liver therapy was not as was expected.

One patient, a female, aged fifty-two, with a typical history and blood picture of pernicious anæmia, after five weeks' treatment with liver extract, developed a pyelitis and rapidly went down hill and died. At autopsy an extensive pyelonephritis was revealed and the diagnosis of pernicious anæmia was confirmed by both macroscopical and microscopical findings.

Chart II represents the cell counts in another case, a female, aged seventy.

This patient, after an early improvement, shown both clinically and in the red cell count, had three severe attacks of colicky pain in the upper part of the abdomen, accompanied by rigor and followed by jaundice. Originally a delayed direct Van den Bergh reaction was given by the patient's serum, but after these attacks an immediate direct reaction was demonstrated. The leucocytes increased from 4,000 to 15,000 per cubic millimetre and there was an increased number of metamyelocytes (see Chart II). It was thought that possibly the patient had a stone in the common bile duct. After a stationary period of three

TABLE III.

Disease.	Number of Cases.	Pijper's Diffraction Micrometer.		Eve's Halometer.		
		Average Diameter of Halo in Millimetres.	Average Width of Spectrum in Millimetres.	Average Reading.	Maximum Reading.	Minimum Reading.
Normal	50	80	20	4·8°	5·0°	4·5°
Blood diseases:						
Pernicious anæmia	22	66	16·5	4·1°	4·30°	3·90°
Myeloid leuchæmia	7	80	20	4·8°	4·9°	4·65°
Lymphatic leuchæmia	6	76	19	4·6°	4·9°	4·4°
Polycythæmia	4	80	20	4·8°	4·9°	4·8°
Splenic anæmia	3	75	18	4·4°	4·6°	4·4°
Familial acholuric jaundice	3	90	22·5	5·42°	5·6°	5·3°
Acquired acholuric jaundice	1	—	—	4·45°	—	—
Hæmophilia	1	74	20	4·35°	—	—
Purpura hæmorrhagica	1	83	20	5·1°	—	—
Glandular fever	1	80	20	4·8°	—	—
Carcinoma of stomach	9	78	19·5	4·7°	5·1°	4·4°
Carcinoma of colon and rectum	8	78	19·0	4·8°	5·0°	4·45°
Malignant disease in other organs	44	78	19·5	4·7°	5·05°	4·4°
Tuberculosis	58	78	20	4·9°	5·2°	4·6°
Syphilis	4	80	20	4·7°	5·0°	4·5°
Chronic infections and intoxications	11	80	20	4·6°	5·0°	4·6°
Acute and subacute infections	12	78	20	4·6°	4·85°	4·6°
Anærobe infections	3	78	21	4·45°	4·6°	4·4°
Post-hæmorrhage and inanition	7	80	20	4·6°	5·0°	4·5°

to four weeks her condition improved and a good response to liver therapy was evident.

Figure III represents various white blood cells as seen in Giemsa stained films.

The most immature cell of the granular series of cells is the myeloblast. This cell is characterized by a deep blue, rather fragile cytoplasm and a relatively lightly stained nucleus with a fine chromatin structure and several nucleoli.

The next cell in the series is the promyelocyte which has an exactly similar nucleus and cytoplasm except for the development of granules which are at first situated at the edge of the nucleus and are rather coarse and azurophilic. As the cell becomes more mature, the cytoplasm becomes less deeply basophilic and the nuclear chromatin more densely stained. The myelocyte has a full complement of granules in the cytoplasm and these granules are differentiated into neutrophilic, eosinophilic and basophilic. The neutrophilic granules are usually basophilic and are scattered throughout the cell, giving the cytoplasm a uniformly speckled appearance. The eosinophile granules are much larger, of uniform size and packed closely together. The basophilic granules are very coarse, of irregular size and distributed unevenly. The metamyelocyte is a transition cell between the myelocyte and mature polymorphonuclear cell. Metamyelocytes are classified into young metamyelocytes, in which the nucleus is just indented or kidney-shaped, and band metamyelocytes, in which the nucleus is relatively smaller and has an irregularly shaped single lobule.

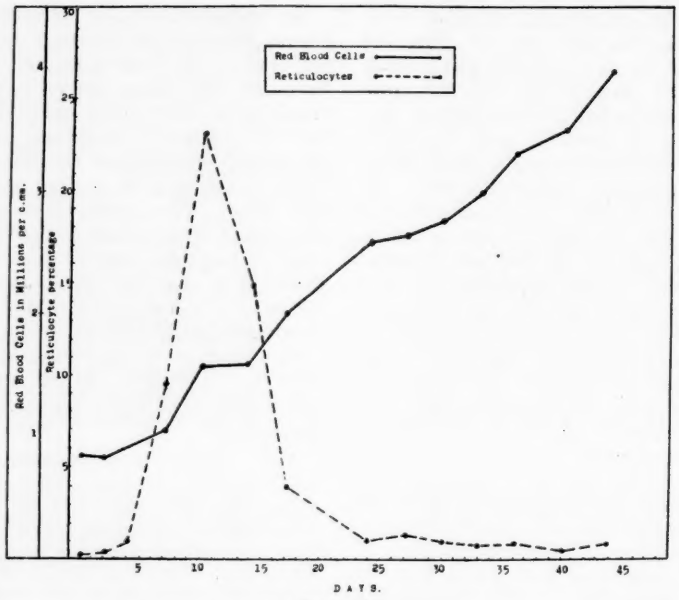

CHART I.
Showing red cell count and reticulocyte percentage in a case of pernicious anæmia treated with liver extract.

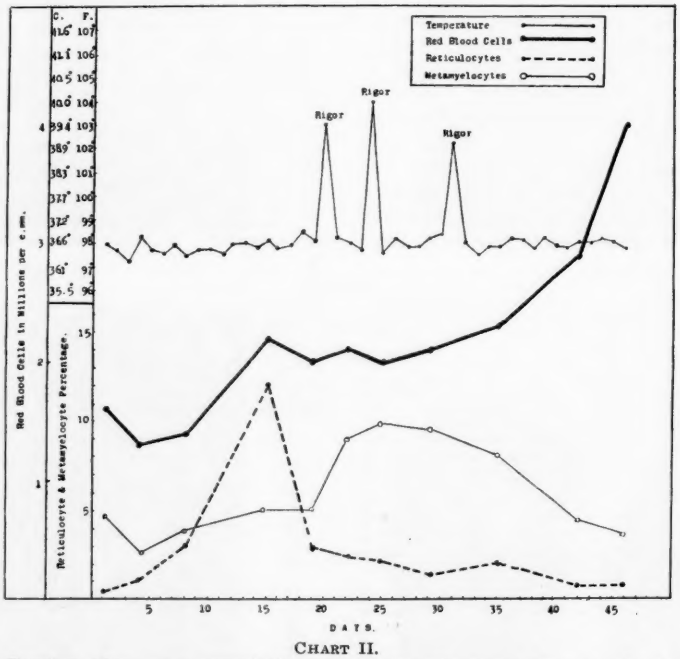

CHART II.
Showing effect of a complication (probably gall stones *plus* associated inflammation) in inhibiting the response to liver therapy in a case of pernicious anæmia.

The mature polymorphonuclear cell is characterized by a multilobular nucleus, the relative amount of nuclear material to cytoplasm being much less than in the immature predecessors. The polymorphonuclear cell may be classified into several groups, according to the number of nuclear lobes. In Arneth's classification there are five main groups and many subsidiary groups. The formula for normal blood is fairly constant and is shown in Table IV. Cooke[18] has modified Arneth's classification by applying a more rigid definition as to the identification of any particular cell. He considers that a fine thread or connecting band of chromatin must be obvious between the lobes and, adopting this criterion, the classification of polymorphonuclear cells is as shown in Table IV.

In certain abnormal conditions, notably in infections in which there is a greatly enhanced leucocyte output, there is an increased number of immature white cells thrown out into the circulation and the cells of Groups I and

II of Arneth's and Cooke's classification are increased. This is called a nuclear shift to the left.

TABLE IV.

"Index."	Class I.	Class II.	Class III.	Class IV.	Class V.
	%	%	%	%	%
Arneth	5	35	41	17	2
Cooke	10·9	25	46·7	15·3	2·1
"Shift to the left" in a case of pneumonia	66	28	5	1	—
"Shift to the right" in a case of pernicious anæmia	6	18	38	26	12

The converse appears in pernicious anæmia where hypersegmented cells are present in the blood, and this increases the number of cells in Group V. This is termed a shift to the right.

The shift to the left is the most important manifestation in disease and Schilling has simplified the classification and made it more adaptable to clinical interpretation. He enumerates the metamyelocytes, both the young and band forms, and any increase in these cells has the same significance as a shift to the left in Arneth's index. Schilling has made wide clinical use of this formula and claims that information of great importance from diagnostic and prognostic points of view can be obtained.

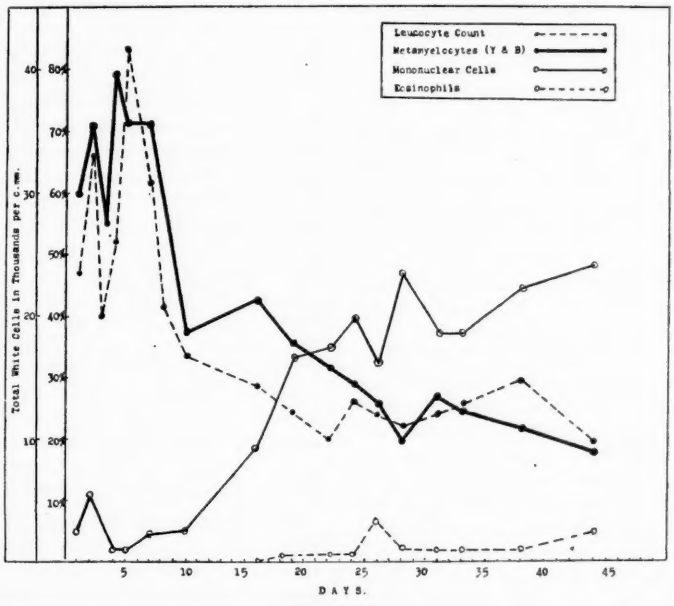

CHART III.
Showing the "nuclear shift" in a case of pneumonia and also the leucocyte count and percentage of mononuclear cells and eosinophile cells.

The following two cases, quoted by Schilling,[19] are of interest in illustrating the application of this method in the diagnosis and prognosis of obscure cases of peritonitis.

In the first case a man, aged forty-two, developed obscure abdominal symptoms after a hernia operation. The blood picture showed a very marked nuclear shift, yet the temperature and pulse were within normal limits. Two days later a diagnosis of peritonitis was obvious and was confirmed at operation, which showed a pelvic abscess. There was distinct improvement after operation, which was shown by a progressive decline in the nuclear shift.

In contrast to this case was that of a man, aged sixty-four, who developed signs and symptoms of an abdominal condition diagnosed as gastro-enteritis. The blood examination revealed a very high nuclear shift and, despite a fairly normal pulse rate and only a slight increase in temperature, Schilling considered the condition to warrant surgical intervention. However, the surgeon would not consider any other diagnosis than gastro-enteritis and when eventually the abdomen was opened on the sixth day of illness, diffuse peritonitis from an old appendiceal abscess was discovered. The day after operation the blood picture showed an extremely high nuclear shift, indicating a hopeless prognosis, which was realized by the death of the patient a few hours later, although his clinical condition did not suggest such an outcome.

Chart III shows the change in white cell count and metamyelocytes in a case of pneumonia.

This patient was under the care of Dr. Major who collaborated with me in this investigation. The patient had a left basal consolidation and after seven days the temperature came down by lysis and remained more or less normal from the fourteenth day of illness; this corresponds to the tenth day on the chart.

It will be observed that at this period the nuclear shift, that is, the percentage of metamyelocytes, showed a marked fall and subsequently that fall was progressively maintained. The percentage of metamyelocytes varies as the total white cell count. Correlated with the fall in nuclear shift, there was an increased number of mononuclear cells. These were predominantly small lymphocytes and this lymphocytosis was associated with the reappearance of eosinophile polymorphonuclear cells. These two findings indicate a favourable prognosis and are associated with a good convalescence.

The question of the mononuclear cells of the blood is an extremely interesting one. The question is very much in a state of flux and one can be dogmatic on only a few points. First, the monocyte described by Naegeli is a definite entity with a characteristic morphology (Figure III). It is a large cell with a lightly stained nucleus, usually indented and exhibiting a characteristic linear arrangement of the nuclear chromatin; the cytoplasm is a grey-blue colour and contains numerous fine granules giving a positive oxydase reaction. Secondly, the small lymphocyte is a cell with a deeply stained nucleus showing ill-defined chromatin masses and surrounded by a narrow rim of basophilic staining cytoplasm often exhibiting a few azurophilic granules. Between these two well defined cell entities there is a rather motley group of cells with varying morphology and vague origin. This intermediate group consists of the so-called large lymphocyte, the hyaline cell, the large mononuclear, the non-granular monocyte and certain definitely atypical cells, such as the Türk cell and the plasma cell. A non-granular cytoplasm distinguishes this

group of cells from the monocyte. In infectious mononucleosis, undulant fever and such like rarities, large mononuclear cells apparently belonging to this category are in the ascendant. The application of special methods, such as the oxydase test and supravital staining, helps a lot in investigating the large mononuclear cells of the blood. The oxydase reaction has fallen somewhat into disrepute of recent years, owing to the fact that it does not distinguish myeloblasts from lymphoblasts, as was originally claimed. However, it is certainly a useful supplementary test in the identification of the monocyte.

By supravital staining is meant the application of basic dyes to living cells. The usual dyes are neutral red and Janus green and the concentration of these dyes has to be so adjusted for any particular preparation that they will be taken up into the cytoplasm and yet cause no mortal injury to the living cell. Figure IV represents supravitally stained cells arranged in a scheme based on Sabin's conception of the development of the white blood cells. Cunningham, Sabin and Doan[20] consider that all white blood cells originate from reticular cells which develop through a primitive cell into myeloblasts, lymphoblasts or monoblasts and thence along the usual lines to the mature white cells. According to these investigators, the myeloblast, lymphoblast and monoblast are distinguished by characteristic grouping of the mitochondria. The mitochondria are tiny rod-shaped or coccus-like bodies present in the cytoplasm of all immature cells and stained by Janus green. In the myeloblast they are distributed fairly evenly throughout the cell, while in the lymphoblast there is a marked tendency for clumping. In the monoblast the mitochondria are grouped in the indentation of the nucleus. The granules of myelocytes are stained by the neutral red and these neutral red granules increase in number as the cell becomes more mature, while the Janus green stained mitochondria diminish. The polymorphonuclear cell in vital preparations shows a full complement of neutral red granules and exhibits active amœboid movement. In the development of the lymphocyte a few neutral red granules appear in the cytoplasm, but these granules are never manifest to any great extent. The monocyte is characterized by a rosette of neutral red granules in the indentation of the nucleus. Sabin states that this rosette cell is identical with Naegeli's monocyte. This statement is disputed by McJunkin[21] who, while agreeing that the monocyte has a rosette of neutral red granules, holds that other large mononuclear cells manifest such a reaction. I am in accord with McJunkin, for in a case of glandular fever I found cells present which were definitely not monocytes and which gave a typical rosette of neutral red granules with supravital staining.[22] Cappell,[23] who has been working with supravital stains for the last year or two, has concluded from a recent research that lymphocytes may develop into cells giving typical rosette of neutral red granules, and ultimately into macrophages.

Witts,[24] who followed a similar line of research, was unable to find evidence of the development of lymphocytes into macrophages, but he stressed the similarity of supravitally stained lymphocytes and small macrophages, and it is possible that Cappell has confused these two cells. Witts concluded that it is probable that monocytes take on the characteristics of macrophages on leaving the blood stream.

It is evident that there is much confusion as to the precise nature and relationship of the mononuclear cells in the blood stream and in the tissues, and, despite the light shed upon the problem by the vital method of staining, our knowledge of these important cells is as yet imperfect.

In conclusion I should like to stress the essential unity of the hæmatopoietic tissue and the blood. The delicacy of the adjustment whereby the cellular composition of the blood under normal conditions is maintained at a constant level, is at present beyond comprehension; probably it is based on chemical changes. It is evident, however, in disease that any gross change in the hæmatopoietic tissue is represented in the peripheral blood. This point was illustrated in experiments on acute lead poisoning in rabbits that I recently carried out. Immediately after an injection of lead there was a leucocytosis, essentially a neutrophilia, in the peripheral circulation. At the same time the bone marrow was packed with the granular precursors of the polymorphonuclear leucocytes. The red cells were heavily depleted in number, but regeneration, as shown by a reticulocytosis, was not in evidence until seven to eight days had elapsed. At the corresponding time the bone marrow showed an intense hyperplasia of normoblasts.

In recent years the typical blood picture in pernicious anæmia has been correlated with changes in the bone marrow. Zadek[25] has studied bone marrow obtained by biopsy in pernicious anæmia cases and found that the megalocytosis in the peripheral blood was coexistent with a hyperplasia of megaloblasts in the bone marrow. Peabody also greatly extended our knowledge of this disease by an investigation along similar lines. He found that during a relapse the bone marrow showed an extensive proliferation of megaloblasts with an absence of the usual normoblasts, while the development of a remission was associated in the bone marrow with a great increase in normoblasts. Peabody[26] explained the anæmia of the relapse as being due to a functionally inefficient bone marrow resulting from the failure of the megaloblasts to differentiate towards mature red cells, while the blood picture in the remission is explained by the resumption of a more normal type of cell development with an increased production of normoblasts, as is indicated by the reticulocytosis in the peripheral blood.

The restoration of a permanent remission by feeding with liver, kidney or beef predigested by

normal gastric juice, or according to Wilkinson,[27] normal gastric juice or desiccated stomach would indicate that a specific substance is necessary for the normal maturation of red cells in the bone marrow and that the substance is lacking in patients who develop the Addisonian type of anæmia.

Summary and Conclusions.

1. Red cell counts do not correctly indicate the extent of an anæmia unless the blood volume remains constant and, if plasma volume is maintained at a constant level, the total blood volume in conditions in which there is a depletion of red cells must of necessity be lowered.

2. The ordinary clinical methods for the estimation of hæmoglobin are subject to marked experimental error, which is particularly evident with the Tallquist method.

3. In estimating the significance of leucocyte counts, the time factor must be considered in view of the physiological diurnal variation.

4. The measurement of the diameter of red cells by the halo method can be satisfactorily applied to the diagnosis of pernicious anæmia and possibly familial acholuric jaundice.

5. The megaloblast which is found characteristically in pernicious anæmia films, develops into the megalocyte and can be distinguished from the progenitors of normal red cells by the size of the cell and the structure of the nucleus.

6. The response of pernicious anæmia to liver therapy is not invariable, but may be inhibited by the presence of sepsis.

7. Schilling's index is useful in the diagnosis and prognosis of obscure cases of sepsis.

8. The monocyte and the small lymphocyte are readily identified by a characteristic structure, but other mononuclear cells apparently in an intermediate group are classified with difficulty, even with the aid of the oxydase reaction and supravital staining.

9. There is an exact correlation in the morphology of bone marrow and blood.

10. Pernicious anæmia is apparently a deficiency disease in which some substance, essential for the normal development of red cells, is lacking.

Acknowledgement.

I wish to thank Mr. Sutherland, who constructed a diffraction micrometer for me.

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SOME BLOOD CONDITIONS.[1]

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IN presenting this paper I would say that I have not attempted to give in full detail or even touch on all the points of importance in connexion with the diseases referred to. I intend to refer briefly to some interesting recent work on platelets, but apart from this my remarks will be based chiefly on certain cases of clinical interest that I have met in practice.

First of all I propose to speak briefly about certain aspects of pernicious anæmia.

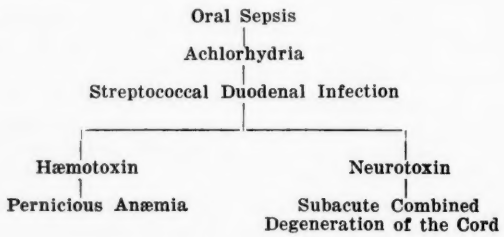
Pernicious Anæmia.

Probably the chief point of interest about pernicious anæmia during the last three years has been the search for what may be called the X substance responsible for the great success in treatment of this disease since Minot and Murphy taught us the value of liver or kidney feeding. Castle has shown that feeding with beef that had been predigested with normal gastric juice, either in a normal stomach or *in vitro*, was followed by improvement comparable with that of liver feeding, and in consequence of his investigations and the success obtained by certain minimal quantities of liver, the suggestion was made that the disease was due to an imperfect gastric juice being unable to extract from the proteins of the food some essential antianæmiac substance, thus assuming it might be a deficiency disease. Lately Wilkinson,[(1)] investigating a small series of cases, has confirmed some of Castle's work and has also obtained excellent results by feeding patients with hog stomach, both fresh and in a desiccated form. The same good result has been obtained by giving either mucous membrane only or the muscular coat only, thus tending to prove that the peptic enzyme factor is not the essential one. He also found that meat predigested by hydrochloric acid and commercial pepsin was of no value.

Of these various meats, liver, either as such or as extract, is the common substance used in treatment of this disease and compared with the older methods of treatment, there can be no doubt of its great value in the vast majority of cases. Time only will tell us its ultimate value.

That it has already had a great immediate effect, apart from our clinical observations, tends to be proved by the investigation carried out by McKinlay,[(2)] working for the Medical Research Council. He has made an exhaustive analysis of the death rates from pernicious anæmia since 1920 in England and Wales. He shows that there was practically a fairly standard mortality rate for all those years, including 1927, in which year liver feeding first began to exercise a slight influence. Towards the end of that year the rate showed a slight decrease, but for the year ending 1928 there was a very striking decline in mortality, 915 deaths less than expectancy (1,854 as against 2,769 expected) and he states that this affected both sexes, but was limited chiefly to the young adult and middle ages.

Much discussion has taken place as to the effect of such treatment on subacute degeneration of the cord, many denying that liver is of any benefit in such cases. Lately I noted that Carmichael had examined eleven patients at Saint Bartholomew's Hospital and failed to find proof of any real improvement. We all know that in pernicious anæmia it is common to get ill-defined evidence of cord involvement and although, in view of later developments, it may prove necessary to modify it, Hurst's conception of the disease in 1925 was briefly as follows:



Accepting this view of the ætiology, one can easily conceive of some patients presenting predominantly a picture of pernicious anæmia and others of cord involvement, the latter not usually showing any marked degree of anæmia, either in appearance or in the blood examination. In London I found a fairly uniform insistence on the point that the latter cases were cases of subacute combined degeneration of the cord from the onset, that is, the neurological signs and symptoms were the reasons for the patient seeking advice, and predominated throughout.

Knowing that the cord has no power of regeneration and with a toxin exerting an early and marked influence on the cord, one can easily understand such patients having actual degeneration of many posterior and lateral column fibres at an early stage of the disease, and no treatment would restore function in those fibres.

It may well be that it is these "primary" subacute combined cases that do not respond to liver therapy. Even a demyelinated fibre can function for a time at least, but, short of demyelination, one can still get very definite evidence of interference with function of fibres of the posterior and lateral columns and yet a return to almost normal function, with liver treatment, as is shown by the following case.

Mrs. O. suffered from pernicious anæmia and subacute combined degeneration of the cord. She came under observation on May 22, 1927, and presented the following signs and symptoms: Dyspnœa, slight icterus, anæmia and tingling of hands and feet. She then had loss of sense of position. No reaction was given to the Wassermann test and an examination of the gastric contents revealed achlorhydria. After blood transfusion the patient showed general improvement. She was seen again on August 23,

[1] Read at a meeting of the Victorian Branch of the British Medical Association on July 2, 1930.

1928, when she was admitted to hospital. There was general weakness, but especially of the legs, in which she also complained of stiffness. She felt as if she were standing on a padded floor and could not walk, mainly owing to ataxia. The following were the main findings:

Examination of the blood revealed the following:

Erythrocytes, per cubic millimetre ..	2,100,000
Leucocytes, per cubic millimetre	2,200
Hæmoglobin value	43%
Colour index	1·12

Examination of the film revealed anisocytosis and poikilocytosis, many megalocytes and an occasional macronormoblast.

On examination of the nervous system the lower limbs manifested slight spasticity and paresis of both legs. The knee jerks were present on the right and also on the left side. The ankle jerks were absent on both sides. The plantar reflexes were extensor in type.

The vibration sense was lost on both sides. The position sense was much impaired on both sides. Sensation to pin prick and cotton wool was diminished on both sides.

Treatment consisted of dilute hydrochloric acid, liver half a pound daily, and coordination exercises for legs.

On September 8, 1928, both right and left plantar reflexes were equivocal and on September 22, 1928, they were both flexor. She was then walking with the aid of a stick. Her red blood corpuscles equalled 5,000,000 and the blood film showed slight anisocytosis only.

I wish also to refer to the duration of treatment by liver. It has always been known that pernicious anæmia is a disease particularly prone to remissions and that between attacks many patients have long intervals of comparatively or quite good health. During these intervals it usually happened that no special treatment was required. Now we have a very potent remedy that often causes a rapid and progressive rise in the number of red corpuscles, and I firmly believe that frequently the new treatment does not require to be continued once the blood picture has been restored to something near normal. Probably many patients will then remain stabilized on smaller or less frequent doses or even without any liver for varying intervals of time. I think this consideration is important, not only because by causing hyperfunction of the bone marrow we may be "whipping a willing horse," but also because some laymen are only too ready to treat themselves without judgement and control. Nobody at this early date can speak definitely of the possible ill effects of persistent unnecessary liver (as such or as an extract) feeding, but I believe the therapy may be overdone. It would be strange if such were not the case. In *St. Bartholomew's Hospital Reports* published this year[3] it is mentioned that thrombosis, gout, one case of acute nephritis and one of uræmia have been reported by different observers as occurring during liver therapy and a definite rise above the average normal red cell count has been noted by several. I have noted the last on several occasions and will refer to one patient who may be an example of what I have just mentioned, the ill effect of over-treatment. I am not giving full notes of this patient, but the slide shown will give the essential features. The blood examination on August 15, 1928, caused me to take readings of her blood pressure again, with the interesting results set out in the accompanying table.

TABLE SHOWING RESULTS OF TREATMENT OF MRS. M. R., AGED THIRTY-NINE YEARS.

Date.	Red Blood Corpuscles.	Blood Pressure in Millimetres of Mercury.		Therapy.
		Systolic.	Diastolic.	
26/10/27		114		On liver half pound daily.
30/10/27	3,400,000			
28/11/27		126		
9/1/28	3,800,000			
20/5/28	5,100,000			Liver reduced to half pound on alternate days.
15/8/28	7,000,000 (H.B.=82%) (C.I.=0·58)	162	112	Liver reduced to half pound twice weekly.
17/9/28	6,000,000	150	100	Liver reduced to quarter pound twice weekly.
22/10/28	4,600,000	135	90	
3/12/28	4,080,000	135	85	Half pound thrice weekly.
17/12/28	5,000,000			

At this stage I lost touch with the patient.

I am not going to make the rash assertion that the higher blood pressures were the result only of the higher red cell counts. So many factors, some known and others unknown, enter into the ætiology of hypertension. In this patient I could find no other reasons for the rise and the higher blood pressure estimations were carefully checked by my house physician and myself; in addition, the pressure fell as the number of red cells decreased.

I do suggest that treatment during the remission should be limited or stopped temporarily, according to the red cell count, and that the younger patients may respond more readily to therapy and so be more liable to some degree of polycythæmia.

Acholuric Jaundice (Familial or Acquired).

Acholuric jaundice was first described by Minkowski in 1900. The main distinguishing features of the congenital type of the malady are: Hereditary history, anæmia, icterus of the hæmolytic type, enlargement of the spleen, microcytosis, abnormal fragility of the red cells.

The most important and most constant diagnostic feature is the lowered resistance of the red corpuscles to varying strengths of salt solution. Normally red cells are preserved in physiological saline solution for a considerable time. When red corpuscles are added to a series of saline solutions of varying strengths below that of physiological saline solution, it will be seen that hæmolysis, laking, begins to appear in a solution of 0·44% of salt in water. The more hypotonic the solution, the more laking occurs, till at about a strength of 0·34% of saline solution hæmolysis is complete. In this disease hæmolysis starts in saline solutions of a higher strength than 0·44 and therefore the red blood cells are definitely more fragile than normal.

Added to this abnormal fragility of the red cells is the fact that they are smaller than normal. With vital staining, large numbers of reticulocytes can be demonstrated, up to 30% of the red cells, although from time to time the percentage may vary very much in any one case. Piney considers that the

periods of much hæmolysis, as evidenced by increased jaundice, correspond with the increased numbers of reticulocytes. Normoblasts are also to be found.

C.C., aged fourteen years, was admitted to the Alfred Hospital on January 1, 1929. He had never been robust, always anæmic and prone to breathlessness at games. He was subject to "attacks" of weakness usually accompanied by increase in pallor and jaundice, pain mostly referred to the splenic region and some vomiting, necessitating rest in bed for four or five days. He was very ill on admission and required transfusion of blood.

On examination later it was found that his spleen extended to 7·5 centimetres (three inches) and his liver to 5·0 centimetres (two inches) below the costal margin He gave no reaction to the Wassermann test.

On January 8, 1929, examination of his blood gave the following findings:

Erythrocytes, per cubic millimetre ..	1,800,000
Leucocytes, per cubic millimetre	14,000
Hæmoglobin value	17%
Colour index	0·5
Reticulocytes	26%
Platelets, per cubic millimetre ..	130,000

Film examination revealed anisocytosis, poikilocytosis and microcytosis, polychromatophilia and many normoblasts. In the differential white cell count 74% of the cells were polymorphonuclear cells, 5% myelocytes and 8% metamyelocytes. Hæmolysis began at a strength of 0·6% of saline solution.

On February 18, 1929, blood examination showed:

Erythrocytes, per cubic millimetre ..	2,500,000
Leucocytes, per cubic millimetre	7,000
Hæmoglobin value	37%

The family history was as follows: His paternal grandfather is said to have had an enlarged spleen. His paternal uncle had an enlarged spleen and anæmia. His father has an enlarged spleen. His elder brother, aged nineteen years, has definite icterus, an enlarged spleen extending 7·5 to 10·0 centimetres (three to four inches) below the costal margin and in a fragility test hæmolysis began at 0·55% of saline solution. His younger brother, aged twelve years, is also affected and his history is given briefly later. He has one sister, aged twenty-two years, who has no jaundice, no enlargement of the spleen and in her case hæmolysis commenced at 0·4% of saline solution.

On February 26, 1929, splenectomy was performed by Mr. St. Clair Steuart.

On microscopical examination of the spleen the Malpighian corpuscles and trabeculæ were well marked. The sinuses and stroma were packed with blood cells in all stages of degeneration. There were numerous hæmosiderin granules free and in phagocytic cells.

On March 11, 1929, his erythrocytes numbered 2,600,000 and his leucocytes 6,000 per cubic millimetre. The hæmoglobin value was 40% and the film showed a few normoblasts and some anisocytosis. He was then discharged from hospital much improved.

His subsequent history is as follows. He kept very well till September, 1929, when he contracted scarlet fever, followed by nephritis, the resultant albuminuria finally disappearing about Christmas time. Since then he has felt very well, can play games like other boys, and his parents say he appears a normal boy.

On June 2, 1930, his liver did not extend below the costal margin and a blood examination was made with the following result:

Erythrocytes, per cubic millimetre ..	4,900,000
Leucocytes, per cubic millimetre	4,500
Hæmoglobin value	90%
Reticulocytes	0·3%

The film showed very slight anisocytosis and poikilocytosis. There were no nucleated red cells, but apparently there was a marked increase in platelets. In the test for fragility hæmolysis began at 0·6% and was complete at 0·46% of saline solution.

I am indebted to the Pathological Registrar, Dr. Phillips, for doing this test, and to Dr. McLean, working in the Baker Institute, for repeating it five days later, their separate findings being similar. This remark applies also in the case of this patient's brother, G.C., aged twelve years, whose story I give briefly as follows:

His history was very similar, though the "hæmolytic crises" had not been so severe. He was slightly icteric, his liver extended five centimetres (two inches) and his spleen 7·5 centimetres (three inches) below the costal margin. Hæmolysis began at 0·55% of saline solution. Splenectomy was done on June 4, 1929, by Mr. A. F. Maclure and on June 2, 1930, he claimed to be very fit and well and full of energy. Blood examination then gave the following findings:

Erythrocytes, per cubic millimetre ..	4,800,000
Leucocytes, per cubic millimetre	5,200
Hæmoglobin value	90%
Reticulocytes	0·2%

Film examination showed a slight anisocytosis, a relative lymphocytosis and there were no nucleated red cells.

In the fragility test hæmolysis began at 0·7% and was complete at 0·44% of saline solution.

We see, therefore, that there is very definite evidence of hyperfunction of the bone marrow, and also of excessive destruction of these fragile red cells as shown by the secondary anæmia and the pigmentary jaundice due to the bilirubinæmia.

It is equally certain that the spleen is the site of the excessive hæmolysis and that splenectomy is followed by its cessation. After such operation the number of reticulocytes rapidly falls to normal, although a return to quite normal fragility does not necessarily occur, especially in the acquired form of the disease. I emphasize the last point, for the statement is made that the only permanent effect of splenectomy in man seems to be a definite decrease in fragility. Thursfield[4] states that in all his cases that he has been able to follow up for more than one year, the fragility has become normal after the lapse of some months or a year. This is not the case with the two boys I am reporting, neither of whom, twelve and sixteen months respectively after the operation, manifests any very definite change in this respect, although complete hæmolysis requires a more hypotonic solution than before.

Much discussion has taken place as to whether in this disease the spleen is the primary factor, the patient suffering from splenic hyperfunction, the overactive organ thus causing a weakening or destruction of normal red cells brought to it, or whether the primary fault lies in the myeloid tissue, the latter giving out a more delicate cell which the spleen deals with accordingly. We believe that normally the spleen destroys red cells that are becoming effete, and here I may mention Botazzi's experimental work from which he claims that the red cells, after passing through the spleen, that is, those in the splenic vein, are normally more fragile than those in the splenic artery. He calls this the result of a hæmocatatonistic action of the spleen. However, an excessive action of this nature can hardly account for the happenings in this disease.

for one would then expect splenectomy to be followed by a rapid return, not only to a normal fragility, but also to a normal size of red cell.

It is stated by Piney that there is no microcytosis in the acquired form of the disease nor apparently is the acquired form transmitted.

In both forms there is a distinct tendency to the formation of gall stones of a pigmentary type and the possibility of such a condition being present must be remembered when the question of splenectomy is under consideration.

It is obvious, of course, that all patients do not require operation, and even in the family mentioned the eldest brother and the father have enjoyed sufficiently good health to enable them to avoid the risk of a major operation.

Purpura.

The other condition I wish to speak about is purpura, the term applied to certain hæmorrhagic conditions which manifest themselves especially by bleeding into the skin and from the mucous membranes. The hæmorrhages, petechial or otherwise, have a varying ætiology, but in the present state of our knowledge it may be convenient to classify the purpuras into two main groups, primary and secondary. In the primary group is placed Werlhof's disease, more commonly known as *purpura hæmorrhagica* and better as essential thrombocytopenia. In the secondary group, an increasing class as the causes become known, we have a large number of conditions which may cause purpura, and they may be conveniently placed under one of two headings: (i) Conditions definitely accompanied by a diminution of blood platelets; (ii) conditions in which the platelets are not necessarily diminished to any great extent, but in which the endothelium of arterioles and capillaries is damaged by toxins or bacteria and by certain drugs.

Recently I went through the records at the Alfred Hospital of admissions for purpura during the last seven years and made notes of those patients diagnosed as suffering from Henoch's purpura, in which bowel hæmorrhage is a feature, Schönlein's purpura or *peliosis rheumatica* in which there is pain and sometimes swelling of joints. and *purpura hæmorrhagica*.

The first two are most common in children under the age of twelve years and many of my colleagues must have had much more experience of them than myself. I believe they are not entities, but merely convenient labels to be affixed according to the signs and symptoms present. Both are the result of an infection and the same infection may cause either Henoch's or Schönlein's disease and the supposed distinguishing features may overlap in the same patient. The latter, of course, has been noted repeatedly.

In my own and in the hospital cases during these years there was some definite febrile condition present in all, except in one hospital patient who had been ill for fourteen days before admission, and in whom no record of his temperature prior to admission was obtained. In those in whom a white cell count was done, there was a leucocytosis of from 10,400 to 22,600 per cubic millimetre, the highest being in a case of mixed Henoch's and Schönlein's disease. At least three patients demonstrated purpuric rash with pain and swelling of joints *plus* abdominal pain with melæna.

It is also not uncommon to find petechial, purpuric and urticarial rash present in the one patient.

Essential Thrombocytopenia or Purpura Hæmorrhagica.

Of essential thrombocytopenia or *purpura hæmorrhagica* there were several supposed cases, but unfortunately a study of the records compelled me to conclude that the diagnosis had not been definitely established.

Apart from hæmorrhage the essential findings in this conditions are: (i) Platelet deficiency, (ii) prolonged bleeding time, and (iii) the clot is characteristically non-retractile and less adherent than normal. There are no other blood changes, for any anæmia present is secondary and appears to be due entirely to the hæmorrhage, and it is not an aplastic anæmia, for bleeding is followed by definite evidence of marrow activity.

The resistance of the capillary walls is also diminished so that a constriction applied to the arm, insufficient to obliterate the pulse, is apt to be followed by skin hæmorrhages within a few minutes. Often, also, there is some splenic enlargement. The disease is more common in females and often there is evidence of some infection at the onset. Varying explanations of the pathology have been given, one being that the spleen exerts a thrombolytic effect, destroying blood platelets to an excessive degree, and this view, coupled with the enlarged spleen, has caused splenectomy to be a recognized method of treatment in the more severe cases. The operation is always followed by a marked increase in the number of platelets which does not in many cases persist, the number often falling later on to much below normal, although the general clinical improvement tends to be lasting. This fact, the fall in the platelet count, is adverse to the view that the spleen is the site of the trouble and it is known that the amount of the bleeding is not necessarily proportional to the deficiency in platelets, so the thrombocytopenia cannot be solely responsible for hæmorrhage. Still, the spleen may be responsible for continuous and excessive removal of the platelets.

Nevertheless, other factors must be considered, and especially the permeability of the capillary walls and Bedson's experimental work has shown that abnormal permeability may be the primary cause of hæmorrhage and the blood platelet deficiency secondary to this.

In a perusal of the literature one or two points of much clinical interest emerge. The disease is not necessarily purpuric. Hæmorrhages, for example epistaxes, from any mucous membrane may be the sole manifestation of the complaint, but of interest also is the fact that such conditions as

hæmatemesis and menorrhagia may be the only complaint of the essential thrombocytopenic patient.

Splenectomy.

Before concluding I would refer briefly to certain points related to splenectomy, especially as much work has been done in recent years on blood platelets.

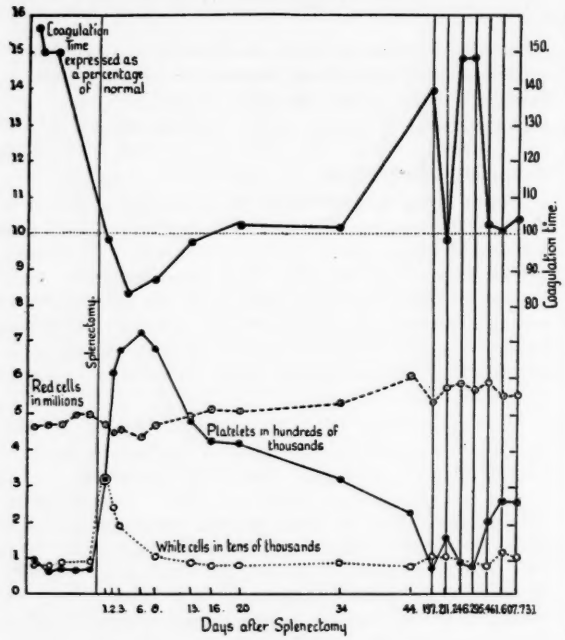


CHART I.

Showing blood changes after splenectomy in patient with *purpura hæmorrhagica*, taken from a paper by Evans in *The Journal of Pathology and Bacteriology.*

First, the possible disadvantages of splenectomy. Necessarily there is an operation risk, but fortunately the spleen does not appear to be a vital organ for the reason that other parts of the reticuloendothelial system apparently can carry out some at least of its duties in a fairly capable manner.

Very little is known about the functions of the spleen. We know that it is concerned with the process of digestion and that it is a storehouse for vast numbers of red cells that can be liberated into the general blood stream when occasion demands, as shown experimentally in carbon monoxide poisoning, repeated bleedings and exposure to the rarefied air of high altitudes *et cetera.*

Also experimentally and clinically there is little doubt but that it plays an important part in the defence reactions of the body, but it is stated that the only constant and permanent effect of splenectomy seems to be a definite decrease of fragility of red cells to saline solutions. This is not the case in my experience.

Secondly, the effects of splenectomy on: (i) Red corpuscles. There is usually a rise in the red cell count in cases in which the spleen is removed for disease or abnormal function of that organ. (ii) White corpuscles. There is apparently always a definite temporary leucocytosis closely following operation, due mainly to increase of polymorphonuclear cells. (iii) Platelets. It has long been known that splenectomy is followed by a temporary and sometimes by a permanent increase in the number of platelets. This fact, of course, is largely the reason for the comparative success of the operation in Werlhof's disease. But in other conditions for which splenectomy may be performed, this rise may be a source of danger. Platelets are an essential factor in coagulation and a rise in the number corresponds usually with a decrease in the coagulation time, and when this is marked, there is a definite risk of thrombosis.

Rosenthal[5] and Howell Evans[6] have demonstrated that patients may be classed as thrombocythæmic, that is, with platelet counts about or above normal, or thrombocytopenic, in which the platelet count is definitely subnormal before operation, the latter condition being usually the case in Werlhof's disease. It is of interest to note that after most surgical operations and after parturition there is an increase in platelets reaching a maximum in ten to fourteen days, and that it is about this period that, with the corresponding shortened coagulation time, the risk of thrombosis and embolism appears to be greatest.[7]

In splenectomy the increase of blood platelets post-operatively tends to be greater still, and to

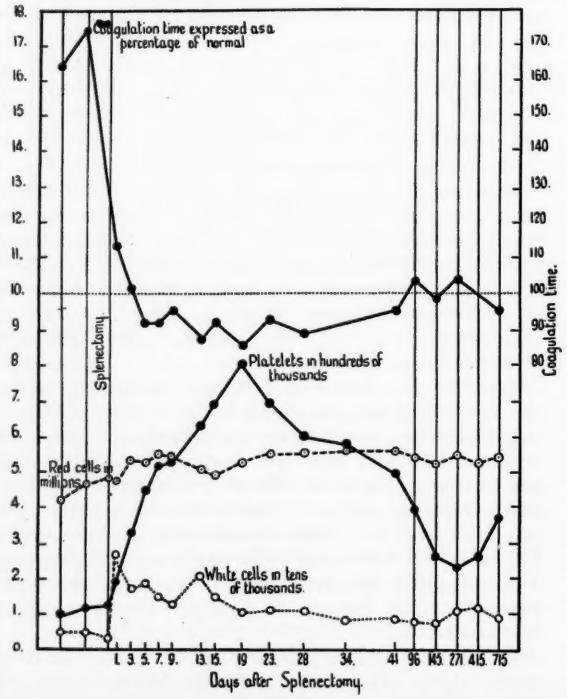


CHART II.

Showing blood changes after splenectomy in patient with splenic anæmia (thrombocytopenic type), taken from a paper by Evans in *The Journal of Pathology and Bacteriology.*

quote Evans[9] "it appears that in the majority of patients exhibiting this thrombotic tendency the platelets before splenectomy are usually normal or increased. There is in these patients a considerable risk after splenectomy of thrombosis which may be fatal."

W. J. Mayo[8] states that in splenic anæmia, of the 10% who died in hospital after splenectomy, the majority died from progressive thrombophlebitis extending from the splenic pedicle to the portal system.

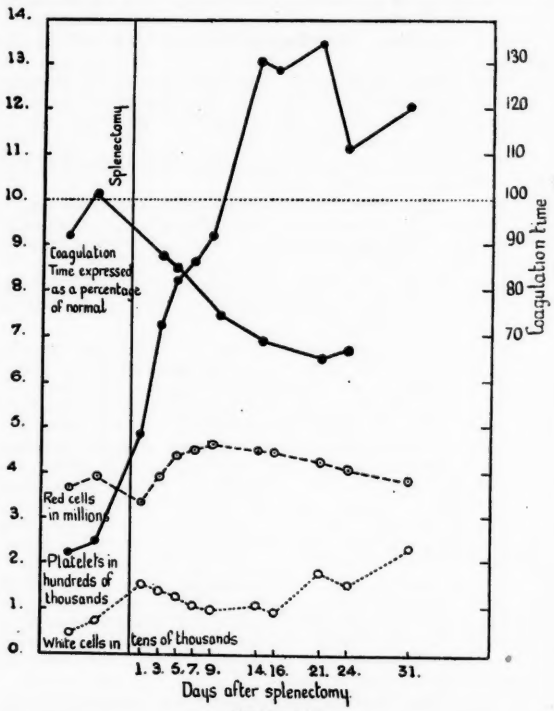


CHART III.

Showing blood changes after splenectomy in a male patient, aged sixteen, suffering from splenic anæmia of the thrombocythæmic type. There was persistent elevation of platelets. Death occurred from mesenteric thrombosis on the thirty-first day. Taken from a paper by Evans in *The Journal of Pathology and Bacteriology.*

It seems to me that a platelet count might well be done as a routine prior to such operations. The information would have some prognostic value and in the thrombocythæmic patients steps might be taken to try to lessen the thrombotic tendency.

In conclusion I show three charts from Evans's paper.[9] The first, Chart VI of Evans's paper, shows in *purpura hæmorrhagica* the rapid rise in platelets, more so than usual, the peak coming about the sixth day, followed by a fall to normal in about thirty days. The second one, Chart X of Evans, shows splenic anæmia (thrombocytopenia). The third, Chart VIII of Evans, shows splenic anæmia (thrombocythæmia). This last demonstrates the rise in blood platelets in a thrombocythæmic patient after splenectomy to about 1,300,000, with mesenteric thrombosis and death occurring at this peak period.

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Reports of Cases.

A CASE OF LYMPHOSARCOMA AND ITS RELATION TO TRAUMA.

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WHEN tumour growth follows quickly on previous injury, the medical referee is often called upon to decide whether the traumatic factor has any relationship to the ensuing neoplastic condition. The case here reported is one such and we considered it of sufficient interest to warrant publication.

History.

A.B., a man, aged twenty-eight years, during the execution of his duties was struck in the neighbourhood of the posterior upper insertion of the trapezius to the skull by the leather belt of a machine.

The following report was received from his medical referee:

> He was bending down at a machine and on coming up he bumped the back of his neck against a belt shifter on a pulley, on August 17, 1928. It was painful at once and three days later a swelling appeared just below the part struck, for example, under the posterior fibres of the sterno-mastoid in the upper part of the posterior triangle.
>
> Examination on October 18, 1928, showed a large swelling, almost half a cricket ball in size, hard, not adherent to the deep structures or to the skin, extending down from the skull down the neck, rounded anteriorly above but elongated below, extending along the outside of the carotid sheath and down to the chest as a string of enlarged lymphatic glands, one the size of a bean and the others the size of peas; it was sensitive in the posterior superior portion and definitely tender below.
>
> A consultation was held with his doctor and diagnosis of sarcoma was given and deep X ray treatment strongly advised.

When seen again on November 20, 1928, the swelling was larger and the enlarged glands were more marked. He was admitted to the Alfred Hospital for deep X ray treatment.

At this time he was found to have a firm swelling at the posterior triangle of the neck, about 7·5 centimetres (three inches) by 5·0 centimetres (two inches) in size, extending down from the site of injury. It was somewhat elastic, with no sign of fluid and lobulated at the lower end, suggesting a mass of glands. In addition there were a few small swellings lower down in the triangle which were definitely recognized as enlarged lymphatic glands. One of these glands was removed to confirm the diagnosis and showed a structure of reticulum celled lymphosarcoma. As it suggested a possible thymic origin, a careful X ray examination of the mediastinum was made, but no evidence of enlarged thymus or mediastinal new growth was found. About this time a complete blood examination was made, but beyond a slight secondary anæmia, no change in the nature, number or proportion of the white cells was found.

Following a course of deep X ray therapy the glands disappeared. During the next six months or so, as the glandular enlargements in the other parts of the cervical, inguinal and axillary involvement became marked, he received further treatment from the X ray department. The condition extended, however, and he was readmitted to the hospital with generalized enlargement of all glands, intense dyspnœa and cyanosis and other signs of mediastinal involvement.

He complained of severe abdominal pain and there were palpable irregular masses in his abdomen. His anæmia became worse and his lower extremities œdematous. He died three months after admission.

His medical referee decided that the case was one for compensation owing to his incapacity following injury, on the following grounds: (i) Definite evidence of injury, namely, the knock at the back of the neck arising in the course of his work; (ii) appearance of swelling close to site of injury shortly afterwards; (iii) possibility of such an injury (*a*) causing activity in preexisting sarcoma, (*b*) precipitating such a development.

Post Mortem Findings.

The patient was a well developed, fairly well nourished and rather muscular young man. His right leg and foot were swollen with œdema and his left leg to a lesser degree. Some enlargement of glands was seen in the neck and in both axillæ. The inguinal regions also showed some enlargement. On cutting the skin the subcutaneous layer, muscles, fascia *et cetera* were found to be very œdematous.

Lungs: The weight of right lung was 1,019 grammes (thirty-six ounces); it was congested and œdematous. The left lung was collapsed, except a small area at the apex. No tumour growth was found in the lungs. Three and a half litres (about six pints) of straw-coloured fluid were removed from the left pleural cavity, also some fibrinous exudate. The bronchi on both sides were filled with dark mucoid material. No sign of tumour growth was found in the bronchial tubes or in the parenchyma. There was no gross involvement of the root glands. A large mass of tumour growth was found at the tip of the pericardial sac and projecting into the left pleural cavity and firmly adherent to the diaphragm. There were numerous small nodules of tumour growth lying subpleurally, especially posteriorly. Some of these were attached to the ribs (see Figure I).

Heart: The heart weighed 339 grammes (twelve ounces). There was no apparent involvement of epicardium or myocardium by the tumour. Slight excess of straw-coloured fluid was found in the pericardial sac. The right auricle was dilated and the right ventricle contained an agonal clot which extended into the vessels. The ascending aorta was rather small in diameter and showed some subintimal orange-coloured fatty deposits, some near the aortic valve but most at the lower end of the aorta and extending into the iliac arteries.

The blood in the vessels was not leuchæmic in appearance.

Pharynx: No lymphoid enlargement was found in the pharynx.

Œsophagus: On surface of the œsophagus there were *post mortem* change and marked congestion.

Stomach: Congestion, but no ulceration or tumour was found in the stomach.

Duodenum: Bile-stained contents were found in the duodenum, but no ulcer or tumour.

Jejunum and Ileum: No affection of Peyer's patches was seen in jejunum or ileum, but scattered subperitoneal nodules of some size were found (see Figure II).

Appendix: The appendix was swollen and pale and in the mesentery, near the tip, an irregular mass of tumour tissue, about 18 millimetres (three-quarters of an inch) across, was found.

Large Intestine: No abnormality was detected in the large intestine.

Liver: The liver weighed 1,698 grammes (sixty ounces). It appeared somewhat congested. No tumour involvement was seen on the external or cut surface and none of the portal glands appeared involved.

Gall Bladder: The gall bladder was much distended with bile, but the ducts were patent.

Spleen: The spleen weighed 127 grammes (four and a half ounces). It was firm; the Malpighian bodies were prominent. No appearances of Hodgkin's streaking or lumps were found.

Pancreas: The pancreas was apparently intact, but all the glands along the upper border were involved by tumour growth (see Figure III).

Para-aortic Lymph Glands: Enlarged masses of irregular shape lay along the aorta from the level of the pancreas downwards and spread along the renal and pelvic branches, especially on the left side. The walls of the iliac veins were invaded and subjected to pressure by the tumour.

Kidneys: In the white mass the right kidney substance was just discernible and the right suprarenal gland was embedded in the tumour at the upper pole. The capsule was greatly thickened and the pelvis was full of tumour growth continuous with that along the renal vessels. The whole mass weighed 679 grammes (twenty-four ounces) (see Figures IV and VI).

The left kidney and suprarenal together weighed 283 grammes (ten ounces). The cut surface was rather pale and swollen, the capsule thickened, and there was some widening and pallor of the cortex. The pelvis showed early hydronephrosis and a mass of tumour growth was found in the perirenal fat.

Suprarenals: The right suprarenal was embedded in the tumour mass and appeared much infiltrated; the left was clear of the tumour and appeared normal.

Brain: The pia-arachnoid was œdematous, but the brain substance showed no naked eye abnormality. No secondary growth was found.

Glands in Axilla: A large mass of irregularly lobulated white tumour growth with indistinguishable outline was found in the axillæ, though more marked on the right side. The tumour everywhere had the same appearance, namely, pale flesh colour, and firm and elastic to the touch. In the right axilla the glands extended as far as the clavicle, to which they adhered.

Inguinal Glands: The inguinal glands were similar to those in axilla, but fewer.

Diaphragm: Many tumour nodules were found on both surfaces of the diaphragm.

Parietal Peritoneum: Much subperitoneal involvement was found.

Pelvis: There was a mass of subperitoneal growth filling up the iliac fossæ, mostly on the right side, and pressing on the pelvic vessels and viscera.

Histological Findings.

A few months before death a gland was removed without difficulty from the posterior triangle of the neck and sent for microscopical examination. The section revealed a condition of great hyperplasia of the reticulo-endothelial

cells and except for a few scattered tiny groups, lymphocytes were absent (see Figure V). The gland was very cellular and the reticulum scarcely perceptible with our methods of staining, namely, hæmatoxylin counterstained with eosin or Van Gieson. Giant cells were not prominent and certainly not in sufficient numbers to warrant a diagnosis of Hodgkin's disease. Eosinophile cells were absent and only a few plasma cells were found. The picture was practically that of endothelioma; but, taken together with the clinical findings, a diagnosis of reticulum-celled lymphosarcoma was given. Ewing separates lymphosarcoma into two types according as the predominating cell is the typical lymphocyte or the reticulum cell. This case agreed with the latter type.

Sections of tissues removed at autopsy showed the following:

Neck Lymph Gland: The capsule of the lymph glands of the neck was thickened and infiltrated. There was complete absence of follicles and true lymphoid tissue was scanty. Stroma was in excess and the contained cells were chiefly of the reticulum cell type, although a few showed multilobed nuclei. Some areas were fibrous and hyaline and regions of necrosis were found where the cells had lost their staining power.

Nodule in Small Intestine: The peritoneal coat of a nodule in the small intestine was still intact. The subperitoneal vessels were dilated and congested. The outer muscle layer was invaded and fragmented by the tumour. The inner muscular layer was entirely replaced by tumour which invaded the submucosa. The tumour extended to the lumen and was covered internally by a layer of necrotic unrecognizable tissue. At the edge of the tumour patch, lying between the *muscularis mucosæ* which limited the healthy mucous membrane, were numerous dilated and congested veins and capillaries. The thickness of the intestine at the site of tumour was three times that of adjacent healthy tissue. These areas appear to have been solitary glands, but the normal lymphocyte found there in health was entirely replaced by the reticulo-endothelial type and the reticulum which in health is not very prominent, was found to be pronounced (see Figure III).

Spleen: The capsule and trabeculæ of the spleen were normal. The Malpighian bodies were well marked and lymphoid in character. In the reticulum of the pulp there were more broken-down red cells than normally found. In the venules and sinuses there was excess of polymorphonuclear cells, but no mononucleosis. There was no tumour condition found on microscopical examination.

Liver: The liver was somewhat cirrhotic. Fibrosis was present in excess around the portal areas and less prominent between the lobules. The liver cells showed marked cloudy swelling in certain areas, but some parts appeared normal with well stained and healthy looking nuclei. Most of the liver cells contained fine granules of hæmosiderin and the Kupffer cells appeared fairly normal. Although there was here and there some small round cell infiltration, no sign of tumour invasion was found.

Kidneys: In the left kidney there was cloudy swelling of secretory tubules. The capsule was somewhat thickened, but only slightly adherent and there was no interstitial fibrosis. The glomeruli were well developed and there was no thickening of Bowman's capsule. Catarrhal changes were present throughout. Everything pointed to recent damage and no infiltration of the organ by tumour was found.

In the right kidney there was much invasion by the tumour *viâ* the pelvis. The medulla was almost entirely replaced by tumour cells, but the cortex showed uninvolved areas. The latter gave the appearance of diffuse nephritis. The tubules were widely separated by rather loose myxomatous tissue and the lining cells were mostly flattened instead of columnar. The glomeruli were extremely anæmic and there were catarrhal changes in Bowman's capsule (see Figure IV).

Lung: In the lungs there were areas of collapse with cloudy swelling and hyaline changes in the cells lining the infundibulum and air sacs. The alveoli contained many large histiocytes loaded with blood pigment. There was much thickening of the pleura over the collapsed areas and the lymph spaces contained much carbon pigment. Other parts of the lung seemed normal except for some increase in interstitial connective tissue along the bronchi and larger vessels. The pleura over normal lung was not thickened. No infiltration by the tumour was found in the lungs.

Pancreas: The parenchyma of the pancreas and the islets of Langerhans appeared healthy. There was excess of fibrous tissue surrounding the ducts, larger vessels and capsule. Invading the capsule at the upper border was a mass of tumour tissue, probably altered lymph glands (see Figure II).

Suprarenals: The right suprarenal body was much infiltrated by tumour and embedded in the tumour mass around the kidney.

The left suprarenal appeared normal except for some hæmorrhages into the cortical substance. No tumour growth was found.

Brain: The cortex of the cerebrum and cerebellum was examined and nothing abnormal was found. No sign of tumour growth was found.

Nodule on Rib: Tumour growth was found invading the thickened periosteum of the rib, but it had not affected the bone (see Figure I).

Heart: Thickened fibrous epicardium and some interstitial fibrosis chiefly following the vessels, and especially in the outer myocardium were found; but except for some damage there, the rest of the heart muscle was healthy.

Mediastinal Lymph Glands: Mediastinal lymph glands contained much carbon pigment. Follicles were well marked and the lymphocytes were normal in character. There were catarrhal changes in the lymph sinuses, but no infiltration by tumour growth was found.

Thyreoid Gland: In the thyreoid there was increased fibrosis. Colloid was plentiful, but stained poorly with eosin. There was thickening of vessels, especially in the adventitial coat. No sign of tumour growth was found.

Discussion.

In the lay mind the idea is prevalent that injury, such as a blow, can start a cancer. Many believe that cancer is the result of previous injury. It seems the rule that the memory must recall some traumatic agency to account for the advent of tumour growth.

A blow on the breast is said to precede the "hard lump" which the surgeon finds on palpation, and a blow or kick on the belly is the acknowledged precursor of carcinomatous conditions in the alimentary tract. Whatever argument to the contrary be used, an unscientific jury[1] is usually ready to make the wish the father of the thought, and in sympathy with the poor unfortunate and his relatives judgement is swayed.

It is, however, quite as unscientific to jump to the other extreme and ridicule the possibility of such a causation of the neoplastic state. All the cards must be put on the table and judged on evidence. The German courts have leaned heavily to the traumatic causation of tumours in dealing out compensation.

What proportion of all malignant tumours can be ascribed to injury? Coley found that out of 970 cases of sarcoma 225 or 23% gave a distinct history of trauma.(1) In nine of his cases the tumour made its appearance a week after the injury and in 117 within a month.

Lowenstein(2) reported that in the statistics of the German Army and Navy 221 malignant tumours were observed in subjects under constant medical attention free from mental bias and that 39 or 16·5% of these were attributed to trauma. Only one malignant tumour was observed to each 15,000 injuries.

In the records of the New York State Industrial Compensation Bureau Lewy found 37 cases of malignant tumours among 26,387 injured persons. This ratio is about the normal incidence of tumours among the general population.

[1] In workers' compensation cases there is no jury.

The relation of trauma to tumour growth assumes great importance when the question of compensation occurs. The necessary evidence that will point to the relation of trauma to tumour is summarized by the French statutes as follows:[2] (i) The authenticity and sufficient importance of trauma; (ii) previous integrity of the wounded part; (iii) a reasonable time relation, three weeks to three years or more in certain cases; (iv) continuity of pathological changes or symptoms in the wounded part and the appearance of the tumour; (v) microscopical proof of the existence of a tumour.

In what way can trauma influence tissue to grow abnormally? What is the effect of trauma? Injury may be slight or severe, long continued or short and sudden. In the case here reported a blow on the back of the neck was considered the originator of the glandular swelling. What would a moderately severe blow do? The skin surface was not broken, but cells and tissues may be separated, some of the injured tissue may die, broken blood vessels allow hæmorrhage into the tissue spaces which must be removed by absorption or phagocytosis *et cetera*, and in the healing process new blood vessels are formed and fibroblastic reaction occurs. This healing by cicatrization means granulation tissue. Quite recently an authority[4] has said that scarring precedes all malignant tumours, and there is certainly a close resemblance between some sarcomata and granulation tissue, and many clinical observations point to the development of sarcomata from granulation tissue.

It may be said that some particular tissue is unstable and that the effect of trauma may be to stir it into a condition of malignant growth. There can be little doubt that crushing injury must disseminate tumour cells and thereby increase the speed of tumour spread; but that injury can so change the character of growth that previously normal tissue can become malignant is less certain.

Cohnheim considered that groups of cells, misplaced during development, may act as the starting point of tumours, and Ribbert went further in this direction by suggesting that tissues exert a certain "tension," having the power of restraining and limiting each other's growth. Thus we might have cells, according to this theory, displaced by trauma and the influence removed which before kept their growth orderly and normal.

Conclusions.

The quick onset of swelling in the neck after the injury would certainly suggest a relationship between the trauma and the tumour development. The relationship of trauma to sarcomatous growth is still debatable.

This case fulfils the requirements of the French statutes except in the case of number 2, that is, the previous integrity of the wounded part. A slight painless swelling of neck glands could easily pass unnoticed by the patient and, as no examination by a medical man had been carried out before the accident, that point must remain uncertain.

Lewy's figures suggest that trauma plays no part in tumour production. If these figures are confirmed from independent sources, and we have to believe that a traumatic history is no more frequent before tumours than it is in healthy persons, then we must abandon it as a causative factor in the present case.

An interesting feature in this case is the absence of involvement of the mediastinal lymph glands. If the traumatic origin be rejected and the abdominal origin accepted, then the tumour condition spreads behind the pleura to the neck, missing the mediastinum.

The necessity for thorough examination of all possible changes in lymph glands is evident and the responsibility of the medical referee is a great one.

From our findings and Lewy's figures we consider that the tumour condition arose abdominally, spreading retroperitoneally along the great vessels in the abdomen, to the right along the renal vessels, upwards behind the pleura to the neck and down along the iliac vessels to the lower extremities.

Thus it appears that the association of the blow to the neck and the development of the tumour was merely coincidence, the injury being received during the early stage of an already present lymphosarcoma. But the possibility must be admitted that the blow might cause activity in tissue of potentially sarcomatous nature or increase the activity of an already present tumour condition.

Acknowledgements.

We thank Professor MacCallum for kindly examining the tissues, both macro- and microscopically, and for his critical survey of the case. We are greatly indebted to Mr. Kennedy for information about the history and treatment of the patient, to Mr. Doutch for his microphotographs, and to Mr. Prosser for the paraffin sections of tissues.

References.

(1) McFarland: "Surgical Pathology," 1924, page 220.
(2) Ewing: "Neoplastic Diseases," Third Edition, page 117.
(3) Ewing: *Loco citato*, page 119.
(4) Auguste Lumière: "*Le Cancer Maladie des Cicatrices*," 1929.

Reviews.

A BOOK ON LOW BLOOD PRESSURE.

NEW ground was broken by Dr. J. R. Halls Dally when he published his book entitled "Low Blood Pressure."[1] The author devotes many pages to the technique of the estimation of blood pressure and its significance. He later formulates what he calls his "biological law," which reads: "Low arterial pressure, whether congenital or acquired, temporary or permanent, is always to be regarded as an expression of low vitality." The so-called "law" cannot be contraverted provided all are agreed upon what constitutes low blood pressure. Dr. Dally adopts the figures of 110 millimetres of mercury as the upper limit of low arterial pressure for males and 105 millimetres of mercury for females, the lower limits being 66 and 62 millimetres of mercury respectively. He regards a differential pressure of 34 to 31 millimetres of mercury as suspect and 30 or below as pathological. The author is careful to distinguish hypotonia from hypopiesis, and hypopiesia is a term he applies to a "condition of congenital or constitutional origin characterized by persistently low arterial pressure without apparent physical abnormality or in association with suboxidation dependent upon physical abnormalities." He regards it as a clinical entity dependent upon an acid base imbalance tending to alkalinity or an alteration of autonomic endocrine equilibrium. Dr. Dally devotes many pages which bear the imprint of much thought and work to the elaboration of the theory he thus enunciates, and quotes extensively many passages from many authors in support of his thesis. We cannot refrain from thinking that the author very frequently has more than a difficulty in preventing himself from confusing his ideas as to what constitutes hypopiesia, hypopiesis and hypotonia. The latter half of the book is devoted to a compilation of blood pressure readings gleaned from the papers and books of very many writers on almost all diseases, acute and chronic, functional and organic, so that it becomes a veritable storehouse of the literature on the subject. The last chapter is devoted to the treatment of low blood pressure, its many varieties and causes.

Dr. Dally is to be congratulated on producing a book upon a subject which has been neglected or forgotten—albeit a very real condition—in the welter of writings on and research into its antithesis, hyperpiesis.

[1] "Low Blood Pressure: Its Causes and Significance," by J. F. Halls Dally, M.A., M.D., B.Chir. (Cantab.), M.R.C.P. (London); 1928. London: William Heinemann (Medical Books) Limited. Demy 8vo., pp. 274. Price: 15s. net.

The Medical Journal of Australia

SATURDAY, NOVEMBER 8, 1930.

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THE BLOOD.

THE papers by Dr. John A. McLean and Dr. J. P. Major, read before the Victorian Branch of the British Medical Association and published in this issue, are contributions of importance and are worthy of careful study. When papers are read at a Branch meeting, the members present often fail to grasp the importance of many of the issues raised—the mind not unnaturally passes over the new subject or the new point of view and seizes what is germane to everyday work. In the present instance almost the whole of the discussion centred round liver feeding in pernicious anæmia. This is, of course, of great practical importance and the possibility of producing noxious effects by overfeeding with liver calls for careful investigation. Dr. McLean's important conclusions in regard to the value of information gained from red cell counts evoked little comment. Chapters might be written on the methods of making blood counts, on the fallacies attendant on blood examination and on the justifiable deductions. This matter cannot be discussed at the moment. Dr. McLean enunciated an important truth which is so obvious that at first sight it should not need emphasis. He stated that we generally regard the blood "as conveying oxygen and food substances to the tissues and carrying away various waste products of cell metabolism and also having a very important function in any defensive reaction of the body." His reference to Professor A. E. Boycott's address to the Section of Pathology of the Royal Society of Medicine in October, 1929, was of an introductory nature. The question is of such importance, however, that further consideration should be given to it.

Professor Boycott started his paper by a statement somewhat similar to that made by Dr. McLean, and then added that the blood may also be thought of "and sometimes more profitably, as a tissue or organ whose chief business it is to be itself and maintain its own individuality." He said that the blood had diseases of its own and mentioned congenital malformations, malignant tumours on the leucocyte side and the corresponding benign tumours as represented in rare eosinophile and neutrophile overgrowth, the benign tumour of splenomegalic polycythæmia and the resemblance of pernicious anæmia to a malignant tumour. Professor Boycott then went on to discuss problems concerning the quantity of red cells—"the size, that is, of the tissue which is made up of the circulating red corpuscles and the cells in the bone marrow (and sometimes elsewhere) from which they arise." For this tissue he coined the new name "erythron." He then discussed hypertrophy and atrophy of the erythron. As a matter of fact, Professor Boycott cannot determine whether the blood is a tissue or an organ.

It must appear on careful consideration that it would be confusing to regard the blood as a tissue. In his opening remarks, as already stated, Professor Boycott referred only to the blood, the circulating fluid commonly regarded as a vehicle for the conveyance of nutriment to the tissues and for the removal of their products for excretion. In his discussion of hypertrophy and atrophy he coined the word erythron. This introduces the blood-forming organs to the new "tissue." It would be most useful for certain purposes to regard the cellular elements of the blood and their foci of origin as a composite whole. The blood, however, consists of plasma as well as cells, and the plasma has a most complex nature, subserves many functions and can be affected in diverse ways. If the blood-forming

organs, the source of the blood cells, be regarded as part of the blood, the blood being a "tissue," it would be but logical to include in this tissue the general tissue fluid of the whole body, for it is from this general tissue fluid that the plasma is replenished when the volume of the circulating blood has been reduced by hæmorrhage. Moreover, if abnormal manifestations of blood cells are to be regarded as constituting a disease of the blood, we must perforce look on any condition characterized by departures from the recognized normally constituted plasma as also indicating a disease of the blood. This would practically lead to the absurd conclusion that all disease is a disease of the blood. Of course, the composition of the blood—cells and plasma—can be varied by many conditions, atmospheric and otherwise, and the accepted normal must present wide variations. The conclusion of the matter is that the use of such slipshod terms as diseases of the blood must be discontinued. Blood is a vehicle. Diseases of the blood-forming organs may be described, or some other acceptable term may be used. By all means let such conceptions as that of Professor Boycott's "erythron" be adopted; this would be likely to clarify our conceptions of polycythæmia, anæmia and so forth. The use of correct terminology will lead to clear thinking and so to a better understanding of disease.

Current Comment.

KETOSIS AND RENAL INEFFICIENCY.

GREAT are the gifts of happiness and usefulness conferred by "Insulin" on those many people who otherwise would be hapless invalids, but of even greater value is the gift of life itself which only "Insulin" is able to bestow on most of those individuals who pass so nearly unto death in diabetic coma. Before the advent of "Insulin" treatment of diabetic coma consisted of the administration of large quantities of alkali in the hope that the toxic acids in the body might thus be neutralized. Fluid was given freely also with the object of "flushing" the kidneys and assisting in the elimination of poisonous substances. These measures were directed at the acidosis and not at its cause. As fast as the acids were neutralized—and it is doubtful whether they were neutralized to any great extent—further ketone bodies were launched into the blood stream by an inefficient metabolism. Though little is yet known regarding the actual process concerned in the production of ketosis and the causation of coma, the discovery of "Insulin" has provided a corrective for the basic error in metabolism, and thus the supply of ketone bodies may be more or less effectively cut off in most instances, the emunctories being left with the task of eliminating the toxic bodies already in the circulation. It must be admitted, however, that deaths still occur in diabetic coma. Why? Possibly the kidney function may provide an answer. The study of the metabolism has been of such overshadowing importance that it has attracted almost all the activities of investigators, to the neglect of the kidneys, the organs which are of paramount importance in the progress or relief of most diseases associated with the retention in the body of toxic substances. The value of the kidneys' efficiency in the relief of acidosis is rated very highly by Alvin F. Coburn who has recently presented his views based on an experience of ketosis gained both before and since the advent of "Insulin."[1] Coburn selected for study 132 patients who were dangerously ill and whose blood carbon-dioxide combining power was less than twenty-five volumes per hundred cubic centimetres. Of thirty patients treated before the introduction of "Insulin" only two recovered. Of ninety-two treated with "Insulin" twenty-seven died. Three of these were moribund when admitted to hospital, death in two instances was due to unexplained causes, six died of intercurrent disease and the remaining sixteen died of diabetic ketosis without apparent complication while receiving "Insulin." It was with the object of determining the factors responsible for death in these latter instances that Coburn undertook his investigation. Though he recognizes the many factors usually quoted as of prognostic importance, such as age, duration of ketosis before commencement of treatment, adiposity, starvation, quantity of blood sugar and blood fat *et cetera,* Coburn, while stressing the importance of renal efficiency, expresses the view that in the alleviation of ketosis the excretion of the toxic bodies may be of greater value than their oxidation. Prior to the advent of "Insulin" the alkaline treatment in some instances appeared to effect a temporary relief. The greatest degree of improvement was observed in those individuals who excreted by way of the kidneys the greatest quantities of acetone bodies. After the introduction of "Insulin" it became the custom to administer only moderate quantities of fluid. With this treatment and despite "Insulin" administration, death in some of Coburn's cases occurred within the first twenty-four hours. Death was preceded by circulatory failure and either anuria or the excretion of urine containing little or no acetone. The administration of large quantities of fluid was sometimes followed by improvement in kidney function, with consequent excretion of large quantities of ketone bodies and subsequent recovery. Coburn believes that all of the sixteen deaths which occurred in his series, were due to functional renal inefficiency,

[1] *The American Journal of the Medical Sciences*, August, 1930.

though he admits that the blood pressure was low in all instances. The possibility of cardiac failure should not be overlooked; Coburn does not discuss the question whether cardiac failure due to intoxication may have preceded the anuria in some instances. It is worthy of note that a number of *post mortem* examinations revealed no abnormality in the kidneys. Ketosis without ketonuria he believes to be of very serious import and a danger signal at times of the approach of anuria. A failure to excrete acetone was observed in fifteen of his patients treated by "Insulin" administration. Five of these died, nine recovered following the recommencement of excretion of ketone bodies in the urine, and one recovered without the occurrence of ketonuria. The disappearance of acetone from the urine preceded anuria in three instances of continuous drainage of the bladder by catheter. But this procedure is notoriously fraught with danger in advanced diabetes. The development of anuria in these three instances can hardly be regarded as a strong argument in favour of the view that cessation of acetone excretion may be an indication of the imminence of complete renal failure. It is obvious, however, that the maintenance of kidney function must be of great importance in acidosis, and there can be little doubt that this function is often affected to a greater or less degree. The urinary sugar not infrequently decreases during coma; as Joslin points out, this may be to some extent due to starvation, but no doubt the so-called renal bloc is one factor. Evidence of kidney damage may be observed almost invariably in the urine of a person suffering from diabetic coma. Red blood cells, casts and albumin are almost constantly present. Joslin has noted that the amount of non-protein nitrogen in the blood may be very great and that it increases on the supervention of severe disturbance of the kidneys. Provided the kidneys are normal before the onset of acidosis, it would appear that any damage they suffer is of a temporary nature. Anuria developed in only three of a series of sixty-three cases of coma mentioned by Joslin; the administration of abundant fluids sufficed to relieve in each instance. The condition has been noted by various other observers who differ in their views as to its incidence and significance. On the whole, most of the evidence appears to point to circulatory failure as the factor of greatest importance in the inhibition of renal function in acidosis.

THE ESTIMATION OF HÆMOGLOBIN.

In view of the findings of Dr. John A. McLean, whose paper is published in this issue, in regard to the experimental error occurring in the ordinary clinical methods for the estimation of hæmoglobin, it may be of interest to draw attention to a recent communication by C. A. Pons and M. Schneider on the same subject.[1] These authors, like McLean, recognize that the methods in use for the estimation of hæmoglobin leave much to be desired. They have studied four methods: the method of Van Slyke, the iron method of Wong, the colorimetric method of Newcomer and their own modification of the last named method. Their modification consists in the use of 2·5 cubic centimetres of diluent (approximately tenth normal hydrochloric acid) instead of five cubic centimetres, and the use of two coloured glass plates glued together. The details of their method are as follows: Twenty cubic millimetres of blood are added to 2·5 cubic centimetres of diluent. These are mixed and allowed to stand for thirty minutes. The blood mixture is transferred to one cup of a colorimeter, distilled water is added to the other cup and the double glass plate is inserted under the latter. The Bausch and Lomb microcolorimeter is used and light conditions are kept uniform by the use of a Palo daylight colorimeter lamp. Pons and Schneider translated the readings of the colorimeter into grammes of hæmoglobin per hundred cubic centimetres of blood by means of a table. It was found that the original Newcomer colour plate method produced results that were unsatisfactory because the colour elicited was "too pale for matching the hues in more commonly encountered ranges." Observations were made on specimens of blood from twenty different persons and determinations were made by each of the four methods. The results are tabulated. The values obtained by the modified Newcomer method vary from those obtained by the Van Slyke method by a minimum deviation of 0·29% and a maximum of 3·90%. The average variation for the twenty determinations was 1·80%. When the modified Newcomer method and the Wong method were compared, it was found that the results obtained by the former approached more closely those obtained by the Van Slyke method in sixteen instances and that those obtained by the Wong method approached more closely those of the Van Slyke method in four instances. Pons and Schneider do not regard these findings as indicating that the modified Newcomer method gives more accurate results, but they hold that the facility of the latter method renders it preferable. It should be pointed out that the normal standard adopted by Pons and Schneider is 15·8 grammes per hundred cubic centimetres of blood, the Haden standard. Haldane's figure was 13·89 grammes and Williamson's 16·8. The figure adopted by Pons and Schneider is in the neighbourhood of that adopted by many teachers. Thus Maxwell, of Melbourne, in his book on clinical biochemistry, assumes 16 grammes to be the normal figure. It may also be noted in passing that Pons and Schneider make the suggestion, a view also expressed by Maxwell, that hæmoglobin values would be more satisfactorily expressed in grammes per hundred cubic centimetres of blood. McLean states that Van Slyke has reduced the experimental error with his method to 0·48%. In view of the claims of Pons and Schneider for their modification of the Newcomer method, it should be put to trial.

[1] *Archives of Pathology*, August, 1930.

Abstracts from Current Medical Literature.

MORBID ANATOMY.

Epidermoid Carcinoma.

R. A. WILLIS (*The Journal of Pathology and Bacteriology*, July, 1930) has investigated the visceral metastases in a series of twenty cases of epidermoid carcinoma of the head and neck. The cases were unselected. All organs were submitted to both macroscopical and microscopical examination. Metastases in the cervical lymphatic glands were a prominent feature in the series. In only four instances were lymphatic metastases absent and the carcinomata in these instances were situated in the lip. The author divides epidermoid cancer into (i) cornifying, squamous carcinoma or acanthoma, (ii) transitional-celled carcinoma, (iii) rodent or so-called "basal-cell" carcinoma. Fourteen of the tumours were acanthomata, one was a transitional-celled carcinoma and five of the tumours consisted of anaplastic, non-differentiated cells of neither squamous nor transitional type. Including with the present series another observed subsequently, the author has found visceral metastases in seventeen of thirty-five instances. In these instances the visceral deposits invariably originated in malignant penetration of the lumen of main veins in the neck. The liver is shown by the author to be the most frequent site of development of visceral metastases. Established visceral metastases often penetrate adjacent veins in a manner similar to that described in the neck. The author refuses to accept the view that all parenchymatous organs are equally fertile as a soil for the development of cancerous deposits. He believes that his series furnishes some evidence that hepatic tissue is a preeminently suitable nidus for the growth of at least the epidermoid cancer cell. He thinks that this may easily be related to the glycolytic power of cancerous tissue demonstrated by Warburg.

Siderosis.

IN discussing the pathology of pulmonary siderosis, Milton G. Bohrod (*Archives of Pathology*, August, 1930) points out that a pathological study of the disease has been made in only about thirty cases, though anthracosis and silicosis have been very thoroughly studied. There are two types of dust containing iron in considerable quantities. The one is found in iron ore mines and in factories in which iron pigments are used. Here the iron is most usually in the form of the oxide. The other type of dust contains particles of metallic iron and also quantities of silicates, and is to be found in metal grinding and polishing shops. Hart has described the occurrence of a type of siderosis due to each of these dusts. In the first, the red type of iron lung, pneumonokoniotic induration predominates, and tuberculosis is rare. In the second, the black type, the induration is less pronounced and tuberculosis is common. The author reports two cases of siderosis illustrating these two types. He gives a full description of the macroscopical and microscopical appearances of the important organs. The patient who had suffered from black siderosis died of tuberculous bronchopneumonia. The lungs affected with siderosis caused by inhalation of iron oxide were also infected with tubercle, but the tuberculous process was of a fibrotic type and limited to the lymph glands. Many macrophage cells were observed. Their object apparently was to transport the iron particles to the bronchial mucous membrane and thence to the sputum or to the lymph nodes. Iron reaching the lymph nodes was either deposited there or else carried on by way of the thoracic duct to the blood stream, to be taken up by the cells of the reticulo-endothelial system. It was observed that only the soluble iron was transported or found intracellularly. The author concludes by remarking that examination of the sputum for the presence of iron may be of value in the diagnosis of the disease.

Experimental Leucoplakia.

A. H. ROFFO (*Revue Sud-Américaine de Médecine et de Chirurgie*, April, 1930) has endeavoured to find an explanation for the preponderating incidence of cancer of the mouth in men as opposed to that seen in women. Acting on the supposition that the condition in man is due to the irritating action of tobacco, he has carried out a series of observations on rabbits. The animals were divided into three groups—ten in a group. In two of the groups the tissues were subjected to previous modification in accordance with the author's ideas of the development of cancer. The gums of the animals were subjected for five minutes each day to smoke produced by the combustion of tobacco contained in a metal syringe. In the first group after twenty-five days whitish plaques with a smooth, raised surface were formed; these animals had no preliminary treatment. The animals in the second group received a preliminary injection of a 5% oily solution of cholesterol; those in the third group received 0·5 cubic centimetre of a colloidal solution of cholesterol. In the animals of the second group there formed a milky white plaque with irregular borders; in most of the animals the lesions took fifty days to develop. On microscopical examination hyperplasia of the Malpighian layer was found and in the peripheral zone there was a horny layer beneath which there were granular cells. In the animals of the third group the appearances were somewhat similar to those seen in the second group: epithelial hyperplasia, the formation of a horny layer at the periphery and the appearance of a granular layer. The author regards the lesions as being produced by the products of combustion of the tobacco and not by the active principles—extracts and nicotine. They are due to the action of resinous substances derived from the oxidation of oils and acids produced by the distillation. They are also due to the products of a double synthesis produced by the raised temperature and formed by the stable benzine nuclei and pyridine bases.

Renal Lesions due to Administration of Irradiated Ergosterol.

THE effects on the kidney tissue of the administration of massive doses of irradiated ergosterol have been studied by Tom Douglas Spies and Eugene C. Glover (*The American Journal of Pathology*, July, 1930). Sixteen young rabbits, each weighing about 2,300 grammes, were used in the experiments. Irradiated ergosterol with an antirhachitic potency 1,000 times that of cod liver oil was administered in a dose of three to ten cubic centimetres at intervals of one to four days, save in one experiment, in which the average interval was five days. Two animals were killed on the fourth day of the experiment, two on the sixth day, and two on the eighth day; the remaining ten were allowed to die from the effects of the irradiated ergosterol. Eight control animals were given similar doses of the solvent oil used in the preparation of the irradiated ergosterol. The kidneys of the animals which had died of irradiated ergosterol poisoning were sometimes slightly reduced in size, but always appeared normal in colour, shape and consistency. When the kidneys had been cut, however, definite changes could be seen. The most apparent changes were observed in the kidneys of those animals which had survived the longest. Innumerable small areas consisting of greyish brown deposits of calcium were dotted through the cortex. The renal arteries of the animals which had survived the longest were sclerosed, but in those which had died rapidly, little or no change was observed in these vessels. The kidneys of the control animals and those which had received irradiated ergosterol over a period of less than nine days, appeared normal in every respect. Histologically the glomerular arterioles and the interlobular arteries were observed to be sclerosed and to be affected with calcification and hyalinization. Many of the most severely damaged arteries were heavily laden with fat, which appeared for the most part in the medial and subintimal regions. The internal elastic lamina was often greatly thickened. In the less damaged kidneys cystic dilatation and little thickening of the basement membrane were observed in the tubules. Later changes in the tubules took the form of calcification and thickening of the basement membrane. The tubules were often distended with large hyaline casts containing calcium. In the severely damaged kidneys the glomerular capsules were often thickened, hyalinized and calcified. The kidney lesions were in all instances accompanied by the presence of large

amounts of albumin in the urine during life and the retention of nitrogen products in the blood.

MORPHOLOGY.

The Union of Epiphyses in Indian Girls.

G. GALSTAUN (*Indian Medical Gazette*, April, 1930) reports the results of radiological investigation into the age at which ossification occurs in Indian girls. Examination was made of hand, wrist, lower ends of radius and ulna, and the elbow joint. In many instances it was difficult to determine whether or not a centre had joined. Union was assumed to be complete when the epiphyseal space had been completely filled in and the bone in epiphysis and diaphysis was of equal density. In all instances it was found that fusion of epiphysis and diaphysis occurred at a considerably earlier age than that quoted by various authorities for the fusion of the same bones in Europeans. Metacarpals and phalanges were found to have fused at ages fourteen to sixteen years, as against seventeen to twenty-one given by various European authors. The lower end of the radius was found to unite with the shaft at the age of fourteen to fifteen years, the lower end of the ulna at about sixteen years. European authorities quote the ages of eighteen to twenty-three years for the union of the same bones. The head of the radius and the olecranon were found to unite with the shafts at an average age earlier by one year than that quoted by Paterson, the most recent authority. The epiphyses for the two condyles of the humerus were observed to have united with the shaft at the ages of thirteen to fourteen years, as against fourteen to fifteen years according to Paterson and fifteen to twenty-two years according to other authorities.

Relation between Plasma Cells and Erythroblasts.

H. E. JORDON (*Anatomical Record*, Volume XLII, 1929) describes the morphology of the plasma cell of Unna and Marschalkó and discusses its resemblance to the erythroblast at various stages of the latter's development. The similarity is particularly noticeable in certain abortive erythroblasts seen in pernicious anæmia. In the rabbit there occur in certain lymph glands abundant plasma cells, of which some become vacuolated. The author suggests that the term "plasma cell" be restricted to this degenerative type. After further argument the author suggests in conclusion that the plasma cell of Unna and Marschalkó represents in part an abortive erythroblast, generally of lymphocytic origin.

Craniometric Studies.

JOHN CAMERON (*American Journal of Physical Anthropology*, Volume XIII, 1929, page 154) records the results obtained from a survey of the breadth-height index in various racial types. This index is obtained by measuring the height of the skull from basion to bregma, multiplying the figure obtained by 100 and dividing the result by the cranial breadth. It was found that in the European, American Indian, Mongol and negro the breadth-height index varied inversely as the cephalic index. The author discovered a sexual factor which appeared to have an effect on the index in all the races observed by him.

JOHN CAMERON (*American Journal of Physical Anthropology*, Volume XIII, 1929, page 171) makes a report of an extensive survey of the cephalic index in diverse racial types of mankind. He found that the index was consistently higher in females than in males, that is, the cranial breadth was greater in proportion to the cranial length in females than in males.

Researches in Craniometry.

JOHN CAMERON (*Transactions of the Royal Society of Canada*, Volume XXIII, 1929, Section V, page 119) describes three new cranial indices. All three indices are for the purpose of showing the degree of prognathism. The first is an index of the relative proportions of the pituitary-nasion and the pituitary-alveolar distances; the second is an index of the relative proportions of the pituitary-nasion and the nasion-alveolar distances; the third is an index of the relative proportions of the nasion-alveolar and the pituitary-alveolar distances. All three indices are highest in the orthognathous type of skull. The first two indices gradually diminish as measurements are made of each mammal lower in the mammalian scale, and a study of the indices reveals gaps in the gradually descending line where there are gaps in the history of evolution. There are no such gaps when the third index only is used.

Transmission of the Sensation of Taste.

DEAN LEWIS AND WALTER E. DANDY (*Archives of Surgery*, August, 1930) record the results of their observations on the course of the nerve fibres transmitting sensations of taste. In 1822 François Magendie divided the trigeminal nerve in dogs and concluded that this nerve was the sole conductor of sensations of taste, but the authors point out that the problem of taste was not to be so readily disposed of. They remark that it is not possible to trace the nerves concerned throughout their courses, hence it has been necessary to employ indirect methods of study, such as clinical and pathological observations, experiments on animals and postoperative observations on human beings. All observers now admit that the *chorda tympani* conducts sensations of taste, but the route traversed by the fibres of this nerve has not been ascertained. The authors discuss the theories advanced by Schiff, Lussana, Ziehl, Eulenburg and Landois and others. Lewis and Dandy studied the effects on the sense of taste of the division of certain cranial nerves in man for the relief of surgical conditions. When tests for the presence of the sense of taste are being applied, great care must be exercised that the material placed on the tongue does not come in contact with the oral or posterior glossal taste buds. Material which stimulates the sense of smell should be avoided, and care should be taken to see that there is no confusion between the senses of taste and touch. Careful observations must be made before operation as control experiments. The authors found no evidence to support the theory that a variable nerve supply conducts the sensations of taste, as was first suggested by Krause. They conclude that one nerve only is concerned, namely, the *nervus intermedius*. The course of the fibres conducting sensations of taste is directly by way of the *chorda tympani* through the geniculate ganglion and *nervus intermedius* into the pons.

Degeneration of the Testes in the Guinea-Pig.

FRED. E. EMERY (*Anatomical Record*, Volume XLIV, 1930, Number 4) has injected trout spermatozoa intraperitoneally into male guinea-pigs. He found that degeneration of the testes with complete absence of spermatozoa in the epididymides occurred in many animals. One testis was retained in the scrotum as a temperature control, then the degeneration of this testis was compared with the other testis of the same guinea-pig and was found to be similar in condition. The author discusses the factors which incur degeneration in the testes, especially in relation to temperature, peritonitis and antibody formation.

The Origin of the Corpus Luteum in the Rat.

E. T. ENGLE AND P. E. SMITH (*Anatomical Record*, Volume XLIII, Number 3, 1929) have made a study of the ovaries of adult rats in which cystic ovaries have been produced by means of fresh transplants of the anterior lobe of the pituitary and this has afforded additional evidence concerning the origin of the *corpus luteum*. It was further found that after the cyst had reached a considerable size, definite luteinization was observed and, moreover, the progress of this phenomenon is more easily followed than in the untreated animal. Prolonged studies showed that lutein changes are seen in both the *theca interna* and the *granulosa* and it was shown clearly that in these cysts the resulting definitive *corpus luteum* is composed of elements from both sources. As the walls of the cyst become gradually replaced by lutein tissue, it then becomes a lutein cyst. It was also observed that the antrum of this cyst is then invaded by the growing cords of the lutein tissue, until the cavity is finally filled. Its greater size is apparently the only evidence that this structure in question is genetically a follicular cyst.

Special Articles on Diagnosis.

(Contributed by Request.)

XVIII.
PERNICIOUS ANÆMIA.

THE diagnosis of pernicious anæmia seldom offers much difficulty, yet it is often overlooked. It demands the systematic collection of evidence which, once collected, is usually easy of interpretation. The examiner's mind, however, must be alert to the suggestion conveyed by the patient's history and general appearance that a case of pernicious anæmia confronts him, in order that the search for diagnostic data may be set on foot. Errors arise much more often from failure to recognize the possibility that the disease is present than from any difficulty in assessing the evidence afforded by the case.

A discussion of the diagnosis of pernicious anæmia must therefore begin with a brief account of the characteristic general features of the disease; the further diagnostic criteria can then be presented in the natural sequence in which they are sought by the clinician.

The General Clinical Picture.

Pernicious anæmia is a disease of middle life; it is seldom seen in persons under forty years of age and is rarer still in those over sixty. Males are slightly more susceptible than females. The general clinical picture is largely that of any severe anæmia, the main symptoms being weakness and loss of energy. The onset is usually gradual; to quote Addison's well worn description: "The disease makes its approach in so slow and insidious a manner that the patient can hardly fix a date to the earliest feeling of that languor which is shortly to become so extreme." By the time the patient comes under observation cardiac symptoms, such as palpitation, precordial pain or distress and dyspnœa on exertion may be prominent. If, as is commonly the case, cardiac bruits and subcutaneous œdema are noted during the examination, a mistaken diagnosis of heart disease may be made. Usually, however, languor and general weakness dominate the clinical picture and their occurrence, especially in a well nourished patient of sallow or lemon-yellow colour, should at once raise the suspicion in the examiner's mind that the case is one of pernicious anæmia. Inquiry will then be directed to the presence or absence of certain signs and symptoms characteristic of pernicious as opposed to secondary anæmia.

Signs and Symptoms Peculiar to Pernicious Anæmia.

Of the symptoms the most characteristic is a history of relapses and remissions. In no other disease are these spontaneous fluctuations in severity so common and the majority of pernicious anæmia patients have experienced one exacerbation at least before coming under medical observation. Symptoms referable to the gastro-intestinal tract are also striking. A history of recurrent sore tongue is often elicited; occasionally it long antedates the onset of general weakness. Diarrhœa, usually intermittent, is sometimes troublesome. Anorexia and vomiting occur less frequently. Paræsthesia of the extremities, giving rise to complaints of numbness and tingling, is very common.

The special physical signs which serve to distinguish primary from secondary anæmias are usually easy of detection. The majority of patients have a lemon-yellow colour of the skin with slight icterus of the conjunctivæ; frank cutaneous jaundice is unusual, but simple pallor is sometimes seen. The tongue may be smooth and red, with prominent papillæ; superficial erosions may occur about its tip and sides. It must be noted, however, that both subjective and objective signs relating to the tongue are frequently absent. In over half the cases the spleen is enlarged; usually the increase in size is such as to render it palpable only on deep inspiration. The nervous signs vary greatly. Although paræsthesia is so common, objective signs are frequently wanting. Careful examination, however, often reveals diminution of vibration sense or of the sense of joint and muscle position in the hands and feet. Occasionally the nervous signs and symptoms are so prominent as to raise doubts whether the condition should not be classified as one of subacute combined degeneration of the cord. Slight fever for which no adequate cause can be discovered, is most suggestive that the anæmia is of the pernicious type. The daily maximum is usually between 37·2° and 37·8° C. (99° and 100° F.), but may be as high as 38·3° C. (101° F.).

The presence of several of these signs and symptoms in conjunction with a suggestive history justifies a tentative diagnosis of pernicious anæmia of which confirmation must then be sought in laboratory investigations.

Laboratory Investigations.

First and foremost amongst these is the demonstration that the anæmia is a macrocytic one. The anæmias which accompany *Bothriocephalus latus* infestation and sprue, are also characterized by macrocytosis, but in this country rare instances of severe anæmia in pregnant women are the only cases which may cause confusion in this respect. In some cases of pernicious anæmia macrocytes are present in such large numbers as to be easily recognized in stained smears. Their detection in this way is, however, subject to many fallacies which careful comparison with the cells of a normal film does not always avoid, and in most instances some method of actually measuring the erythrocytes is necessary. Earlier methods of estimating the size of the red blood cells were so cumbersome and complicated as to render them impracticable in clinical work, but the recent introduction by J. S. Eve of the halometer has made available a simple and easy method of determining whether or not macrocytosis is present. An unstained blood smear on a slide is placed in position and a direct reading on the scale provided can be made within a few seconds. Indirect evidence of macrocytosis is afforded by the finding of a high colour index which indicates that the hæmoglobin carrying capacity of the individual cell is above normal. Clinical methods of determining the hæmoglobin percentage are, however, notoriously inexact, so that while a colour index of 1·5 or thereabouts may be regarded as almost diagnostic, care must be exercised in interpreting figures just above one.

The general findings as regards the number of erythrocytes have an indirect value. "There is," as Osler said, "no other disease which so often reduces the number of red blood cells below two million per cubic millimetre"; and as he also noted: "There are patients with extreme anæmia who are remarkably vigorous." Generally speaking, a patient suffering from secondary anæmia presents much more severe general symptoms than one with a similar grade of anæmia of the pernicious type. The leucocytes and platelets are diminished in number. The important diagnostic features of the stained film are, in addition to macrocytosis, the finding of megaloblasts and the extreme irregularity in shape of the red cells. It must, however, be strongly emphasized that neither of these is characteristic of pernicious anæmia. Both occur in other varieties, but much less commonly, so that their presence has at least a suggestive diagnostic significance.

Very important diagnostic evidence is afforded by the demonstration of a quantity of bilirubin in excess of normal in the blood serum. The simplest and easiest method of doing this is by Fouchet's test. Two drops of the suspect serum are added to two drops of the reagent (trichloracetic acid five grammes, 10% ferric chloride two cubic centimetres, distilled water twenty cubic centimetres). The development of a green colour within five minutes may for practical purposes be taken to indicate a quantity of bilirubin above normal. More exact determinations may be made by Van den Bergh's test which, however, necessitates colorimetric methods not readily available in clinical work. The diagnostic value of these tests is very great in that almost all untreated pernicious anæmia patients give a positive Fouchet reaction or a delayed direct Van den Bergh reaction with a figure of 1·8 or more units of bilirubin. The serum of patients with secondary anæmia, except those the subject of a septicæmia due to hæmolytic streptococci, gives no reaction to

Fouchet's test and yields a figure of less than 1·8 Van den Bergh units.

Last, but not least in importance, is the result of examination by a fractional test meal. Almost without exception patients suffering from pernicious anæmia have achlorhydria. Again, however, this finding is far from absolute in its diagnostic significance. Absence of free hydrochloric acid in carcinoma of the stomach frequently gives rise to confusion and it may, of course, be an accidental accompaniment of many other types of secondary anæmia. Further, *achylia gastrica* may actually be caused by long-continued and severe anæmia of any origin. It may therefore be said that the presence of free hydrochloric acid in the stomach contents practically rules out pernicious anæmia, but its absence is no more than an important single link in the chain of evidence which justifies such a diagnosis.

Therapeutic Test.

In rare instances evidence from all the above sources may still be insufficient to clinch the diagnosis absolutely and an appeal to the therapeutic test of the patient's response to liver feeding may be necessary. The daily administration of 240 grammes (eight ounces) of liver or of an amount of extract equivalent to at least 360 grammes (twelve ounces) of whole liver brings about, in almost every case of pernicious anæmia, rapid clinical improvement and a brisk reticulocytosis which reaches its height about the end of the first week of treatment. It is now clearly established that the administration of liver or liver extract very occasionally fails to benefit patients suffering from pernicious anæmia. These failures, however, are so rare that they do not impair the practical value of the therapeutic test. Secondary anæmia following acute or chronic hæmorrhage responds, but very much more slowly, to liver feeding, especially if iron in large doses is administered at the same time. The anæmias which result from sepsis or toxæmia, are resistant to treatment with liver.

Differential Diagnosis.

The main difficulties in differential diagnosis have already been briefly mentioned. Secondary anæmias can be ruled out by the absence of characteristic clinical signs and by the features of the blood examination. The anæmia which accompanies carcinoma of the stomach, causes most confusion, but it is definitely of the secondary type and is usually associated with positive radiological evidence of the presence of the primary growth. Secondary anæmias with hæmolytic features sometimes give rise to difficulty; for instance, advanced and severe grades of hæmolytic jaundice may superficially resemble pernicious anæmia, but the absence of macrocytosis and the frequent occurrence of increased corpuscular fragility afford a ready means of distinction.

There are three other diseases which are sometimes mistakenly diagnosed in patients suffering from pernicious anæmia. Cardiac disease has already been referred to as a source of error, but it can be readily ruled out by investigation of the blood if the correct diagnosis is suspected by the examiner. Myxœdema and chronic nephritis may also be at first suggested by the general features of the case, but they, too, can be excluded by more careful examination and by simple laboratory tests.

Conclusion.

In conclusion two points may be reemphasized. No single clinical or laboratory finding is diagnostic of pernicious anæmia, but a careful consideration of all the available evidence almost always justifies a confident diagnosis. The more often the disease is suspected, the more often will it be correctly diagnosed; as Cabot puts it: "The incidence in any community is a good deal a matter of keenness on the part of the practitioners."

S. O. COWEN, M.D. (Melbourne),

Physician to In-Patients, Melbourne Hospital; Lecturer in Therapeutics, University of Melbourne.

British Medical Association News.

SCIENTIFIC.

A MEETING OF THE VICTORIAN BRANCH OF THE BRITISH MEDICAL ASSOCIATION was held at the Medical Society Hall, East Melbourne, on July 2, 1930, DR. R. G. MCPHEE, the President, in the chair.

Blood Examination and Blood Conditions.

DR. JOHN A. MCLEAN read a paper entitled: "Blood Cells: Recent Advances in Examination and Interpretation" (see page 623).

DR. J. P. MAJOR read a paper entitled: "Some Blood Conditions" (see page 632).

DR. S. O. COWEN expressed his appreciation of both papers. There were certain points in each to which he wished to refer. In a recent analysis of 50 cases, including 37 hospital patients and 13 private patients, the possibility of doing harm by excessive liver feeding had not been suggested, but the opposite lesson had been illustrated by relapses occurring in patients who had neglected to continue liver feeding.

Four deaths had occurred in the hospital series, one from pyelonephritis with gross pyobacilluria. *Post mortem* both kidneys had been found riddled with pus. This patient had failed to respond to a month's intensive liver feeding. A second patient with focal sepsis had died also in spite of intensive liver feeding. Four other patients had failed to respond to liver feeding over periods of four to six weeks for no discoverable reason and one of these had been given several blood transfusions. *Post mortem* typical lesions of pernicious anæmia had been found, but no signs of septic complications.

These facts introduced an element of caution in prognosis. Two patients presenting signs of subacute combined degeneration of the cord with the blood picture of pernicious anæmia responded well to liver feeding and lost all their signs of gross nervous lesions. Dr. Cowen's impression was that a fair proportion of such patients did lose the signs of organic lesions and a majority lost their distressing subjective symptoms.

Dr. Cowen showed a chart illustrating the results of examination of the blood of a patient who was suffering from a very severe grade of secondary anæmia, and who developed spreading thrombosis from the site of injection of citrated blood at two transfusions. The patient had been exceedingly ill and the prognosis had seemed bad. Liver feeding, together with the administration of large amounts of iron, had led to gradual improvement and later recovery.

Dr. Cowen also showed the graph of the blood findings in a case of thrombocytopenic purpura. This patient had improved after splenectomy and was thought to be cured, but had returned later suffering from her original condition.

It was doubtful if a clinical cure of this condition ever resulted from splenectomy. It seemed that patients always became purpuric when blood platelets fell below 100,000 per cubic millimetre.

DR. LESLIE E. HURLEY joined in appreciation of the papers and said that he had recently observed the effects of liver feeding in three patients suffering from subacute combined degeneration of the cord. In all there had been great improvement, amounting almost to clinical cure, but not the total disappearance of physical signs.

He thought that larger amounts of liver were necessary for these patients than for those suffering from anæmia only. The maximum benefit was obtained from the administration of three-quarters of a pound of liver daily, and this might have to be given for months. In a series of about thirty patients with pernicious anæmia with subacute combined degeneration reported in *Brain*, definite improvement had followed liver feeding in all except those suffering from septic complications. One patient with pernicious anæmia complicated at first by pneumonia and an acute kidney infection, had not responded to liver feeding until the temperature subsided.

Contrary to a statement frequently made, some patients did develop signs of subacute combined degeneration after coming under liver treatment for pernicious anæmia. Some observers had recorded the occurrence of polycythæmia after excessive liver feeding, but Dr. Hurley agreed with Dr. Cowen that the chief danger lay in underfeeding. He did not agree with Dr. McLean that the Tallquist hæmoglobinometer was useless. For some years he (Dr. Hurley) had used it as a routine together with the Sahli method. The results had corresponded closely so long as the Tallquist reading was made immediately the drop of blood had dried. An observer in the Mayo Clinic had found agreement between the Tallquist and Sahli methods in a series of cases with only about 5% of error.

Patients suffering from pernicious anæmia seemed to be especially liable to gall stones and he had seen three in whom pernicious anæmia had been discovered during the period following operation for gall stones. Dr. Hurley went on to say that Professor Cleland, of Adelaide, had sent him the notes of a series of two thousand *post mortem* examinations which showed that the percentage of gall stones in patients with pernicious anæmia was higher than in the rest of the series.

A patient with pernicious anæmia who had an acute attack of abdominal pain was sometimes operated on for supposed gall stones or acute disease of the biliary passages with normal findings at operation. The pain in such cases might be due to a crisis of increased blood destruction producing the acute abdominal symptoms associated with jaundice.

He was interested in Dr. Cowen's use of liver therapy with iron in secondary anæmia. This was of great value, especially if the anæmia had been due to hæmorrhage. Liver feeding had been used first in anæmia of this type. Good results had been obtained also in anæmia of pregnancy.

In the histories of patients suffering from pernicious anæmia certain individual peculiarities could be traced in some cases for years in the past: (i) There was a familial tendency, (ii) the patient bruised easily, (iii) there was a definite facial configuration, indicating an inherited peculiarity, (iv) absent gastric hydrochloric acid had been detected years before sore mouth and tongue and other stigmata of pernicious anæmia appeared. Other members of the same family sometimes showed some of the stigmata, such as absent hydrochloric acid, sore mouth *et cetera*.

In some cases of pernicious anæmia mental changes were the chief sign of the disease and in one such case at least improvement had followed liver feeding.

DR. E. W. GAULT, of the Melbourne Hospital, said that he had been particularly interested in the subject of pernicious anæmia for some months and had been investigating the effects of various new preparations of liver and various substitutes. He was trying an extract of hog's stomach prepared in Melbourne which, if successful, would reduce the cost of therapy from about one pound to five shillings per week. Referring to the association of a pernicious type of anæmia with other diseases, he had seen recently a patient with chronic nephritis and one with carcinoma of the breast in both of whom the blood picture had been typical of pernicious anæmia.

DR. J. F. MACKEDDIE said that while in England he had been struck by the good results obtained by liver feeding of patients suffering from severe nervous phenomena associated with pernicious anæmia. These results occurred even in some old people, especially when liver feeding was combined with the removal, where possible, of septic foci.

Dr. Major in reply said that he agreed with Dr. Cowen that one was faced most often with the problem of how to induce a patient to have sufficient treatment. His warning had been directed to those who tended to overdo the treatment and to the possibility of ill effects arising therefrom.

There seemed to be no doubt that occasionally it was necessary to give more than half a pound of liver daily to get the desired result, and in some places failure to get a response to treatment by liver extract had been due to lack of efficacy of the extract used. Continuing, Dr. Major said that any apparent disagreement between himself and Dr. Cowen regarding the relationship between the number of platelets and bleeding had been due to a misunderstanding, for he had said that the amount of bleeding was not necessarily proportional to the deficiency in platelets. Bedson and others had demonstrated that an absence of platelets did not in itself lead to hæmorrhage so long as the endothelial lining of small vessels was intact. So far, Dr. Major had not found the white cell condition to revert to normal as a result of liver therapy.

In these days there should be no need to controvert the suggestion that tinglings and such subjective phenomena in themselves could be taken as evidence of any cord degeneration and Dr. Mackeddie had already referred to this point. Dr. Mackeddie had also questioned the importance of platelets, and certainly much further work would be required to get a fuller knowledge of the part they played in coagulation *et cetera*. Dr. Mackeddie had asked why the thrombocytopenic patient did not bleed more and to this he could only reply, in view of the former statements, by asking him, why should he?

Dr. McLean in reply said that he had not had a very extensive experience with the Tallquist method for hæmoglobin determination and perhaps he was a little biased, but nevertheless he considered that it was a method which allowed of a very considerable personal experimental error. Of the present clinical methods the Sahli estimation was almost as simple in application as the Tallquist and gave a far more reliable reading.

The therapeutic action of liver in anæmias other than pernicious anæmia was demonstrated in a case of gas gangrene from a gunshot wound. The patient, a boy, aged eighteen, had been treated with gas gangrene antiserum and had made a good recovery from the infection, but as a result of the toxæmia he had become extremely anæmic. A transfusion had been considered necessary, but liver therapy had first been given a trial and in two weeks his red cell count had increased from 2,000,000 to 4,000,000 per cubic millimetre.

With regard to Dr. Gault's question, Wilkinson stated that the reticulocyte response to feeding with hog's stomach was equal to, if not better than, that with liver feeding. Dr. McLean had also been interested in the changes in white blood cells under liver treatment and had made many leucocyte counts and collected a number of films, but as yet he had not had time to do the differential counts. Fleming last year in *The British Medical Journal* had reported a case of pernicious anæmia in which the shift to the right in Arneth's formula returned to normal under liver treatment, and as far as he knew this was the only work which had been done on the subject.

The question of the origin of the blood cells, as indicated by the various hypotheses put forward, was very confusing. The multiplicity of theories—monophyletic, dualistic, trialistic, polyphyletic *et cetera*—showed the extent of their ignorance of this difficult question.

University Intelligence.

THE UNIVERSITY OF MELBOURNE.

THE following information has kindly been submitted by the Registrar of the University of Melbourne.

The annual report of the Dean of the Faculty of Medicine, recently submitted to the Council, refers to the sustained upward tendency in numbers of students entering on the medical course. The recovery from the slump of a few years ago has been so substantial that the number entering the course has now passed the standard which had been reached immediately prior to the war. He also refers to the following matters, namely: The institution of a two-day course of intensive practical teaching in child welfare; an arrangement for strengthening the teaching in organic chemistry in the first year of the course; a decision to institute diplomas in ophthalmology and in oto-rhino-laryngology to provide a higher qualification for those desiring to specialize in these branches of the profession.

The Dean further refers with regret to the comparative failure of the attempt which has been made to get a uniform standard in the Sydney, Melbourne and Adelaide

schools for the master of surgery degree, stating that although at a meeting in Melbourne of representatives of the faculties of all three schools perfect unanimity was reached, the Sydney and Adelaide faculties refused to adopt all the recommendations made by the conference. The position in brief is that Melbourne, which for many years has had a mastership in surgery which has stood very high, is unwilling to have that standard lowered; that Sydney and Adelaide have decided to adopt as alternative methods for getting the M.S. degree examinations in diseases of the eye, of the ear, nose and throat and in obstetrics and gynæcology; that Melbourne believes that it is impossible in these alternatives to maintain the standard which she has already secured in general surgery, and that, therefore, the introduction of the alternatives must lower the degree. Melbourne is accordingly adopting the plan of diplomas for the specialties.

Provision has been made that for the future the examinations for the M.D. and M.S. degrees shall be held half-yearly in March and September. Up to the present they have been held annually only.

Dr. C. H. Kellaway has been appointed to deliver the Mathison Lectures and has selected as his subject "Snake Venom and Immunities."

Dr. A. M. Wilson has been appointed to give the Thalia Roche Demonstrations in Obstetrics.

Correspondence.

THE FUNCTION OF THE GALL BLADDER.

SIR: In your issue of October 4 Dr. Howard Bullock throws doubt on the suggestion that the gall bladder functions as a reservoir of bile. According to him its capacity is only one fluid ounce, whereas the total volume of bile secreted in a day may be estimated as fifty fluid ounces. Yet two paragraphs further on Dr. Bullock admits that inspissation of the bile occurs in the gall bladder—"the bile may be concentrated ten times." This would therefore allow the gall bladder to store one-fifth of the total bile secreted in a day. Such an estimate tallies with the figures, one-fourth to one-fifth, given by Dr. Babkin (Nova Scotia), who writes the authoritative article on the gall bladder in the *Handbuch der Normalen und Pathologischen Physiologie*, Volume III, page 795.

Yours, etc.,

W. A. OSBORNE.

The University of Melbourne.
October 20, 1930.

A WARNING.

SIR: Of late, a young, clean-shaven man of short stature has been of the habit of "borrowing" ether from practitioners in my district and myself. From interviews with his late employer and from personal observations, I have come to the conclusion that he is either drinking or inhaling the ether. He gives as reasons for his requiring the ether that he uses it in etching and cleaning silk. I would urge all fellow practitioners to be on their guard against this strange inebriate.

Yours, etc.,

"LEAVYGREAVE."

Sydney.
October 22, 1930.

Obituary.

NEVILLE BAMANJI GANDEVIA.

WE regret to announce the death of Dr. Neville Bamanji Gandevia, which occurred at Kew, Victoria, on October 19, 1930.

JOHN MILDRED CREED.

WE regret to announce the death of Dr. John Mildred Creed, which occurred at North Sydney, New South Wales, on October 30, 1930.

Corrigendum.

THE INDIGO-CARMINE TEST.

OUR attention has been drawn to an unfortunate error in the last paragraph of the paper by Dr. W. J. Stewart McKay, published in the issue of November 1, 1930. The amount of indigo-carmine used by Dr. Harris is eight cubic centimetres of a 0·8% solution.

AN EXPEDITION TO PORT STEPHENS.

THOSE who love to "get next to nature," will be interested to know that Mr. E. F. Pollock, F.R.G.S., of 7, Carrington Avenue, Strathfield, who personally organized and conducted large parties of nature-lovers to the Great Barrier Reef and Lord Howe Island in recent years, is arranging expeditions nearer home for December and January next. Parties are being formed to camp at Port Stephens, and from that vantage spot to study bird life on the neighbouring islands, lakes and rivers, where penguins, herons and other seabirds abound. Both men and women are eligible for these trips.

Proceedings of the Australian Medical Boards.

NEW SOUTH WALES.

THE undermentioned have been registered under the provisions of the *Medical Act*, 1912 *and* 1915, of New South Wales, as duly qualified medical practitioners:

Anderson, Douglas Joseph, M.B., B.S., 1930 (Univ. Sydney), "Afton," Mitchell Street, Greenwich Point.

Barry, John Patrick, M.B., B.S., 1930 (Univ. Sydney), 6, Church Street, Randwick.

Bell, James, M.B., B.S., 1930 (Univ. Sydney), Balmain and District Hospital, Balmain.

Bradfield, Stanley George, M.B., B.S., 1930 (Univ. Sydney), 23, Park Avenue, Gordon.

Burns, Colin Michael, M.B., B.S., 1930 (Univ. Sydney), 27, Fort Street, Petersham.

Clements, Nathan John, M.B., B.S., 1930 (Univ. Sydney), 66, Arthur Street, Randwick.

Clouston, Thomas Moore, M.B., B.S., 1930 (Univ. Sydney), Tumut.

Cohen, Roy Samuel, M.B., B.S., 1930 (Univ. Sydney), Saint Andrew's College, Newtown.

Connolly, Edward Philemon, M.B., B.S., 1930 (Univ. Sydney), 63, Fairlight Street, Manly.

Costello, Florence Kathleen, M.R.C.S. (England), 1929, L.R.C.P. (London), 1929, 27, Hazelbrook Road, Wollstonecraft.

Cramp, Cameron Oliver, M.B., B.S., 1930 (Univ. Sydney), 13, Birriga Road, Woollahra.

Cunningham, Norman Charles, M.B., B.S., 1930 (Univ. Sydney), 22, Milson Road, Cremorne.

Dittmer, Felix Cyril Sigismund, M.B., B.S., 1930 (Univ. Sydney), Childers, Queensland.

Drew, William Robert McFarlane, M.B., B.S., 1930 (Univ. Sydney), "Clovelly," Greengate Road, Killara.

Flynn, Francis Stanislaus, M.B., B.S., 1930 (Univ. Sydney), 38, Martin Road, Centennial Park.

Medical Appointments.

Dr. E. A. Johnson (B.M.A.) has been appointed a Member of the Advisory Committee under the provisions of the *Hospitals Act Amendment Act*, 1921, South Australia.

* * *

Dr. B. G. Johnston (B.M.A.) has been appointed a Member of the Port Pirie Medical Board, South Australia, under the provisions of the *Workmen's Compensation Act Amendment Act*, 1927.

* * *

Dr. T. C. Kohler (B.M.A.) has been appointed Deputy Quarantine Officer, Wallaroo, South Australia, under the provisions of the *Quarantine Act*, 1908-1924.

* * *

Dr. D. C. C. Sword (B.M.A.) has been appointed Government Medical Officer at Port Douglas, Queensland.

* * *

Dr. C. T. Underwood (B.M.A.) has been appointed Government Medical Officer at Goomeri, Queensland.

* * *

Dr. J. G. Drew (B.M.A.) has been appointed Deputy Commissioner of Public Health and Deputy Inspector, School of Anatomy, from October 23, 1930, pursuant to the provisions of *The Health Acts*, 1900 *to* 1922, Queensland.

* * *

Dr. E. J. Burton (B.M.A.) has been appointed Government Officer at Boonah, Queensland.

* * *

Dr. H. B. Bruce (B.M.A.) has been appointed Honorary Visiting Medical Officer to the Convalescent Home of the Royal Alexandra Hospital for Children, Collaroy, New South Wales.

* * *

Dr. L. H. Ball (B.M.A.) has been appointed a Certifying Medical Practitioner at Melbourne, Victoria, pursuant to the provisions of the *Workers' Compensation Act*, 1928.

Diary for the Month.

Nov. 11.—New South Wales Branch, B.M.A.: Ethics Committee.
Nov. 12.—Victorian Branch, B.M.A.: Branch.
Nov. 13.—New South Wales Branch, B.M.A.: Clinical Meeting.
Nov. 13.—Victorian Branch, B.M.A.: Council.
Nov. 14.—Queensland Branch, B.M.A.: Council.
Nov. 18.—New South Wales Branch, B.M.A.: Executive and Finance Committee.
Nov. 25.—New South Wales Branch, B.M.A.: Medical Politics Committee.
Nov. 26.—Victorian Branch, B.M.A.: Council.
Nov. 27.—New South Wales Branch, B.M.A.: Branch.
Nov. 27.—South Australian Branch, B.M.A.: Branch.
Nov. 28.—Queensland Branch, B.M.A.: Council.
Dec. 2.—New South Wales Branch, B.M.A.: Organization and Science Committee.
Dec. 2.—New South Wales Branch, B.M.A.: Post-Graduate Work Committee.
Dec. 2.—New South Wales Branch, B.M.A.: Hospitals Committee.
Dec. 3.—Victorian Branch, B.M.A.: Annual General Meeting.
Dec. 4.—South Australian Branch, B.M.A.: Council.

Medical Appointments Vacant, etc.

FOR announcements of medical appointments vacant, assistants, *locum tenentes* sought, etc., see "Advertiser," page xvi.

BURREN JUNCTION MEDICAL COMMITTEE, NEW SOUTH WALES: Subsidised Doctor.

CHILDREN'S HOSPITAL, INCORPORATED, PERTH, WESTERN AUSTRALIA: Junior Resident Medical Officers.

HOBART PUBLIC HOSPITAL, HOBART, TASMANIA: Junior Resident Medical Officer.

MACKAY HOSPITALS BOARD, QUEENSLAND: Resident Medical Officer.

SYDNEY HOSPITAL, SYDNEY, NEW SOUTH WALES: Honorary Clinical Assistants.

THE UNIVERSITY OF MELBOURNE, VICTORIA: Stewart Scholars in Medicine and in Surgery.

Medical Appointments: Important Notice.

MEDICAL practitioners are requested not to apply for any appointment referred to in the following table, without having first communicated with the Honorary Secretary of the Branch named in the first column, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

BRANCH.	APPOINTMENTS.
NEW SOUTH WALES: Honorary Secretary, 135, Macquarie Street, Sydney.	Australian Natives' Association. Ashfield and District United Friendly Societies' Dispensary. Balmain United Friendly Societies' Dispensary. Friendly Society Lodges at Casino. Leichhardt and Petersham United Friendly Societies' Dispensary. Manchester Unity Medical and Dispensing Institute, Oxford Street, Sydney. North Sydney Friendly Societies' Dispensary Limited. People's Prudential Assurance Company, Limited. Phœnix Mutual Provident Society.
VICTORIAN: Honorary Secretary, Medical Society Hall, East Melbourne.	All Institutes or Medical Dispensaries. Australian Prudential Association Proprietary, Limited. Mutual National Provident Club. National Provident Association. Hospital or other appointments outside Victoria.
QUEENSLAND: Honorary Secretary, B.M.A. Building, Adelaide Street, Brisbane.	Members desiring to accept appointment in ANY COUNTRY HOSPITAL, are advised to submit a copy of their agreement to the Council before signing, in their own interests. Brisbane Associated Friendly Societies' Medical Institute. Mount Isa Hospital. Mount Isa Mines.
SOUTH AUSTRALIAN: Secretary, 207, North Terrace, Adelaide.	All Lodge Appointments in South Australia. All Contract Practice Appointments in South Australia.
WESTERN AUSTRALIAN: Honorary Secretary, 65, Saint George's Terrace, Perth.	All Contract Practice Appointments in Western Australia.
NEW ZEALAND (Wellington Division): Honorary Secretary, Wellington.	Friendly Society Lodges, Wellington, New Zealand.

Editorial Notices.

MANUSCRIPTS forwarded to the office of this journal cannot under any circumstances be returned. Original articles forwarded for publication are understood to be offered to THE MEDICAL JOURNAL OF AUSTRALIA alone, unless the contrary be stated.

All communications should be addressed to "The Editor," THE MEDICAL JOURNAL OF AUSTRALIA, The Printing House, Seamer Street, Glebe, New South Wales. (Telephones: MW 2651-2.)

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